# DEVELOPMENT OF DECARBOXYLATIVE CROSS-COUPLING REACTIONS

A Thesis Submitted to

(**Academy of Scientific and Innovative Research**)

For the Award of the Degree of

**Doctor of Philosophy**

***In***

***Chemical Sciences***

By


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**November, 2017**

# CANDIDATE'S STATEMENT

I hereby declare that the work incorporated in the present thesis entitled **"DEVELOPMENT OF DECARBOXYLATIVE CROSS-COUPLING REACTIONS"** is original and carried out by me under the supervision of Dr. Ranjan Jana at CSIR-IICB, Kolkata, West Bengal. The thesis is solely submitted to Academy of scientific and Innovative Research (AcSIR) for the award of the degree of DOCTOR OF PHILOSOPHY in CHEMICAL SCIENCES. I further confirm that the results included in this thesis have not been submitted to any university/institution for the award of any degree/diploma.

Asik Hossian 29.11.17

Place: CSIR-IICB, Jadavpur
Date: November, 2017

Asik Hossian
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## CERTIFICATE FROM THE SUPERVISOR

This is to certify that the work incorporated in this Ph.D. thesis entitled **"DEVELOPMENT OF DECARBOXYLATIVE CROSS-COUPLING REACTIONS"** submitted by Mr. Asik Hossian to Academy of Scientific and Innovative Research (AcSIR) in fulfillment of the requirements for the award of the degree of **"*DOCTOR OF PHILOSOPHY* in *CHEMICAL SCIENCES*"** embodies original research work under my supervision. I further certify that this work has not been submitted to any other university or institution in part or full for the award of any degree or diploma. Research material obtained from other sources has been duly acknowledged in the thesis. Any text, illustration, table etc., used in the thesis from other sources, have been duly cited and acknowledged.

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*Dedicated to my*

*Abba, Amma and Apa*

*"Learning gives creativity,*

*creativity leads to thinking,*

*thinking provides knowledge,*

*knowledge makes you great"*

*-A.P.J.Abdul Kalam*

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November, 2017 Asik Hossian

# ABBREVIATIONS

| | |
|---|---|
| $CDCl_3$ | Deuterated chloroform |
| DMF | *N, N'*-dimethylformamide |
| NMP | *N*-Methyl-2-pyrrolidone |
| DMA | Dimethylacetamide |
| DMSO | Dimethylsulphoxide |
| DMSO-$d_6$ | Deuterated Dimethyl sulfoxide |
| NMR | Nuclear Magnetic Resonance |
| FTIR | Fourier transform infrared |
| 1, 10-Phen | 1, 10-Phenanthroline |
| DMAP | 4-Dimethylaminopyridine |
| DCC | *N*,*N'*-Dicyclohexylcarbodiimide |
| MeCN | Acetonitrile |
| DCM | Dichloromethane |
| $K_2S_2O_8$ | Potassium persulfate |
| TBHP | *tert*-Butyl hydroperoxide |
| $H_2O_2$ | Hydrogen peroxide |
| AcOH | Acetic Acid |
| TEMPO | (2, 2, 6, 6-Tetramethylpiperidin-1-yl)oxyl |

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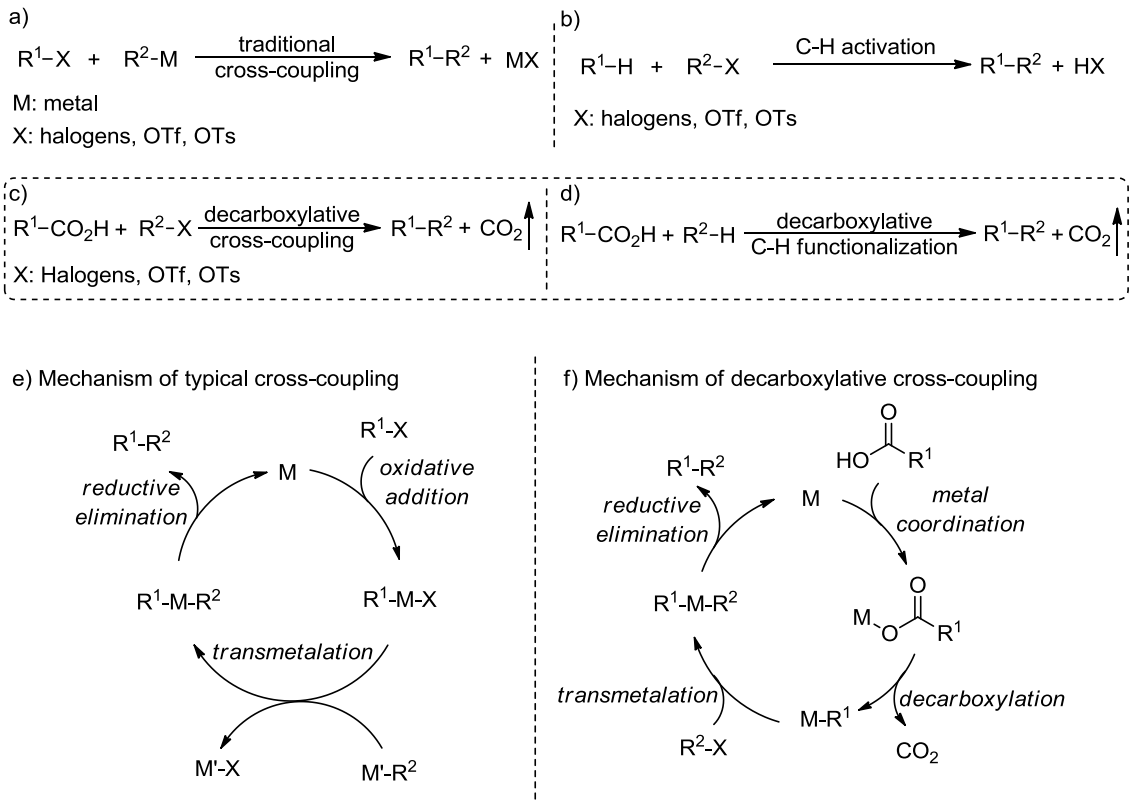
# CHAPTER I

## Transition Metal-Catalyzed Decarboxylative Cross-Coupling Reactions

### I.1. Introduction

Transition metal-catalyzed cross-coupling reactions have been recognized as one of the most powerful tools for the synthesis of natural products, bioactive molecules, polymers, and functionalized materials.[1] Several types of reactions with different organometallic reagents have been reported and widely used to prepare those compounds, such as Kumada, Negishi, Stille, Suzuki, Hiyama, Heck, Sonogashira, and Buchwald-Hartwig coupling reactions.[2] The first five of these reactions consist of the coupling reaction between aryl halides (or pseudo halides) and organometallic compounds bearing Mg, Zn, Sn, B, and Si respectively. These coupling partners have to be prepared from their corresponding simple arenes via multiple steps prior to the coupling reaction.[3] Most of the cases, these organometallic reagents are air and moisture sensitive, therefore special reaction skills and set up is required.[4] To overcome this drawbacks, direct C-H bond activation for coupling reactions have received much attention recently.[5] Several catalysts have been used, including palladium, ruthenium, rhodium, iridium, copper, and others. However, typical C-H bond activation methods require aryl halides or organometallic reagents as one of the coupling partners, which produces stoichiometric metal or acid waste. On the other hand, C-H bond activation methods require installation of the directing groups in the substrates to control site-selectivity and their subsequent removal precludes the synthetic fidelity.[6] As an alternative to conventional cross-coupling or C-H functionalization, decarboxylative cross-coupling has emerged as a modern strategy using readily available and inexpensive; air and moisture stable carboxylic acids as coupling partner.[7] As compared to traditional cross-coupling methods, decarboxylative couplings has several potential advantages; (i) carboxylic acids are ubiquitous and inexpensive reactants; (ii) decarboxylation can provides the reactive intermediates under neutral conditions; and (iii) the only stoichiometric amount of byproduct is $CO_2$, which is nontoxic, nonflammable, and easily removed from the reaction medium. In this case, a mechanistically distinct decarboxylative metalation occurs in lieu of oxidative addition or

transmetalation to form organometallic species which have been used as an alternative to aryl halides or organometallic reagents and subsequently coupled with electrophiles affording the desired coupled products via reductive elimination. However, recently the chemist generates the same organometallic species using some activated carboxylic acid derivatives such as acid chlorides[8], anhydrides[9], esters[10] etc. via decarbonylative process and further coupled with electrophiles. Mechanistically, transition metal undergoes oxidative addition to the activated carboxylic acid derivatives to generate an acyl-metal species. Subsequently, aryl-metal species is formed through the extrusion of carbon monoxide. Moreover, other approaches such as radical photoredox and metal-free decarboxylative coupling reactions are presently under investigation and rapid growth over time.[11]

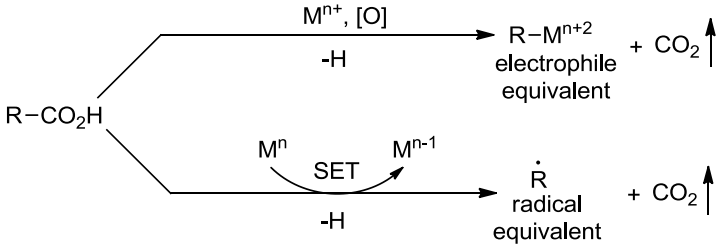



**Scheme 1**. Traditional cross-couplings vs decarboxylative cross-couplings

Very recently, synthetic chemists have applied the *in situ* generated aryl-metal species generated through decarboxylation for the C-H bond functionalization, thus taking full advantage of both C-H bond activation and decarboxylation to develop a novel

synthetic approach, that is, decarboxylative C-H bond cross-coupling reactions.[12] However, there is no exact definition of decarboxylative C-H bond functionalization. Normally, decarboxylative C-H bond cross-coupling reactions refer to these reactions in which carboxylic acids undergo decarboxylative metalation to generate an intermediate that couple with C-H bonds of the other coupling partners to form a new C-C bond. Carboxyl group also acts as a deciduous directing group for ortho C-H bond functionalization, and then subsequent oxidative decarboxylation reactions involved in a stepwise manner under single operation.[13]

Notably, depending on the catalytic system and the reaction conditions employed, carboxylic acids can be used as radical or electrophilic synthetic equivalents of the aryl/alkyl unit for regiospecific cross-coupling reactions.[14]




**Scheme 2.** Generation of coupling intermediates from carboxylic acids

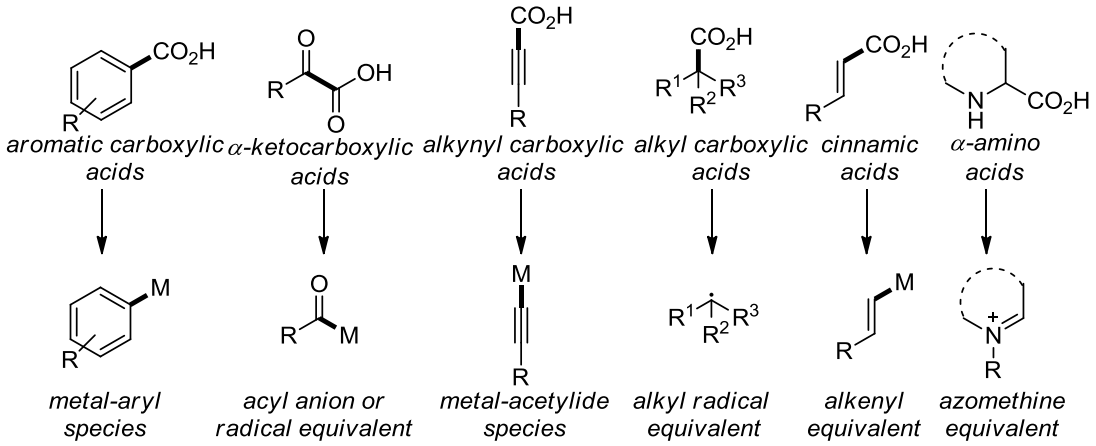



**Figure 1.** Different types of carboxylic acids used in the decarboxylative cross-couplings

There are six types of carboxylic acids have been used as a coupling partner in the decarboxylative cross-coupling reactions- a) the aryl carboxylic acids mainly used for

decarboxylative biaryls synthesis and decarboxylative Heck type couplings; b) *α*-ketocarboxylic acids serves as a acyl anion donor used for decarboxylative ketone synthesis; c) alkynyl carboxylic acids used for decarboxylative alkynylation reactions; d) alkyl carboxylic acids used as $sp^3$-$sp^3$ counterpart in decarboxylative cross-coupling reactions; e) recently, the use of cinnamic acids for decarboxylative alkenylation reactions is also increasing; and f) the *α*-amino acids which are another different class of carboxylic acids to produce azomethine ylide after decarboxylation and used for further *α*-functionalization.[15] The mode of these six types of carboxylic acids is in Figure 1.

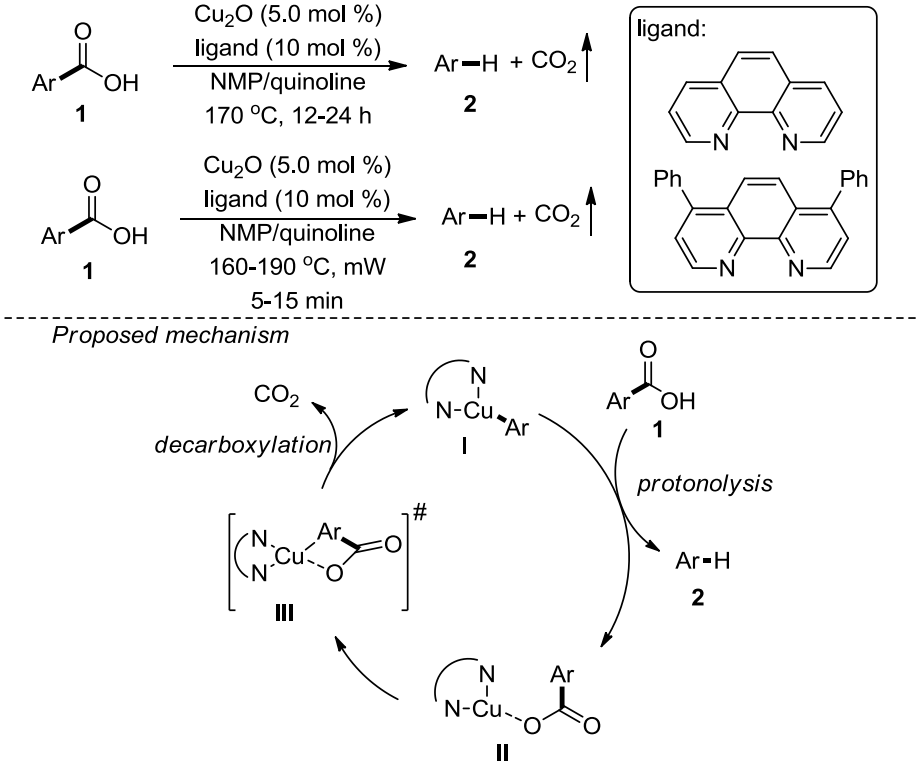
## I.2. Decarboxylative protonation

First, we will discuss about the transition metal-catalyzed decarboxylative protonation or metalation reactions. In decarboxylative protonation reactions, the C-COOH bond is converted to the C-H or C-metal bond through the decarboxylation. This step is the initiation step for all the transition metal-catalyzed decarboxylative cross-coupling reactions.

## I.2a. Copper-catalyzed decarboxylative protonation

Since 1960s, Nilsson,[16] Cohen,[17] and Shepard[18] group reported that some Cu complexes can promote the decarboxylative protonation of aromatic carboxylic acids. But these methods were not practical due to harsh reaction conditions. To enhance copper's ability to influence the decarboxylative transformations further, the Goossen's group developed a copper-catalyzed decarboxylative protonation method using Cu/phenanthroline combination.[19] It has been observed that benzoic acid derivatives bearing electron-withdrawing substituents and/or *ortho* substituents were particularly susceptible to decarboxylation. However, the use of microwave heating can also accelerate the protodecarboxylation process (Scheme 3).[20] Mechanistically, first Cu(I) salt is combined with phenanthroline ligand to form a stable chelate complex. The chelate complex is then coordinate with carboxylic acid generating the Cu(I) complex **II.** A four-membered transition state **III** with carbon dioxide extrusion leads to an aryl-copper(I) species **I**. Finally, the aryl-copper(I) intermediate **I** can undergo protonolysis with acids (or water)

to yield the product and regenerating the copper(I) active catalyst for subsequent catalytic cycles (Scheme 3).

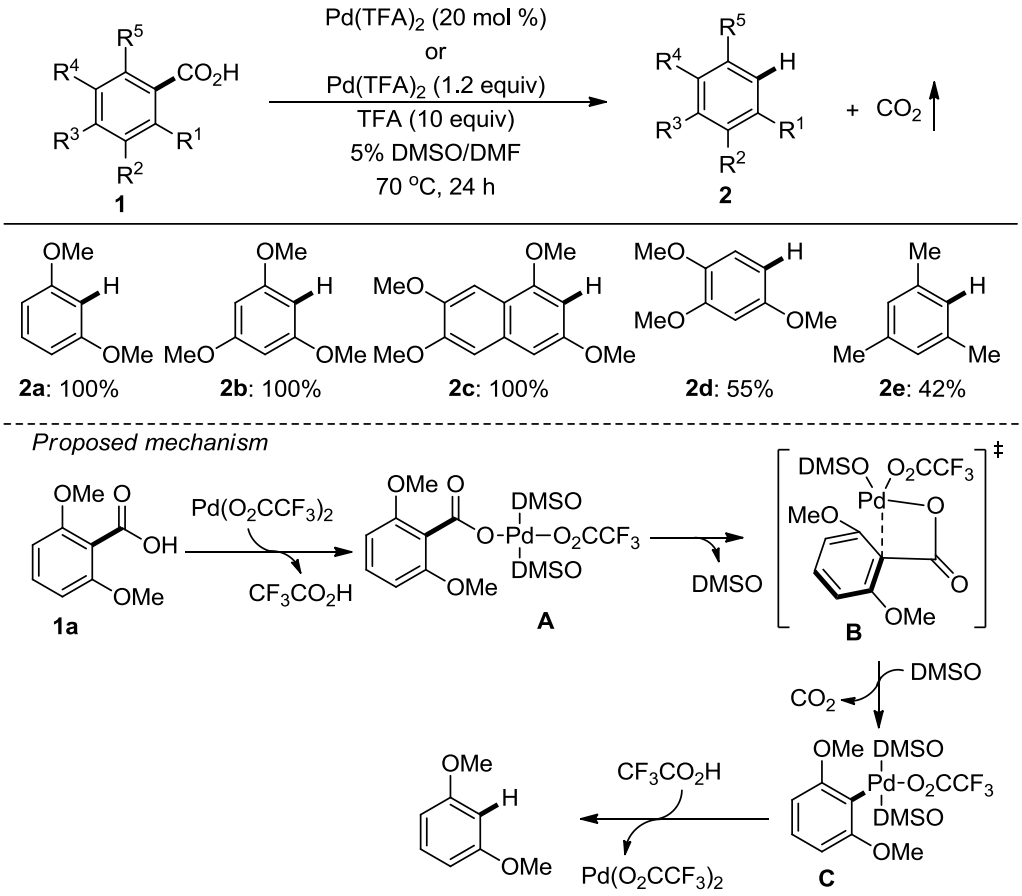



**Scheme 3.** Copper-catalyzed decarboxylative protonation of aromatic carboxylic acids

## I.2b. Palladium-catalyzed decarboxylative protonation

Kozlowski and co-workers[21] reported Pd(II)-catalyzed decarboxylative protonation of aromatic carboxylic acids at 70 °C. The scope of the reaction is strictly restricted to highly electron-rich arene carboxylic acids bearing *ortho*, *ortho*-dialkoxy substituents (Scheme 4). The *ortho*, *ortho*-dialkoxy substituents are essential for this transformation may be due to coordination between oxygen and palladium to stabilize the aryl-palladium intermediate. While this method was extended to mono-*ortho*-substituted or less electron-rich benzoic acid derivatives, a stoichiometric amount of palladium(II) catalyst is required may be due to absence of such type of stabilization in the intermediate and catalytic cycle is not under going for subsequent runs. Mechanistically, they have showed that first Pd(II) catalyst is coordinated with a carboxylic acid generating the Pd(II) complex **A** with the loss of a trifluoroacetic acid molecule. In the intermediate two

DMSO molecule is coordinated with palladium and here DMSO acts as a ligands on the palladium. A four-membered transition state **B** facilities carbon dioxide extrusion generating an aryl-palladium(II) species **C**. Finally, the aryl-palladium(II) intermediate **C** could undergo protonolysis with trifluoroacetic acid to provide the desired protonated product and regenerating the palladium(II) catalyst for next cycle (Scheme 4).

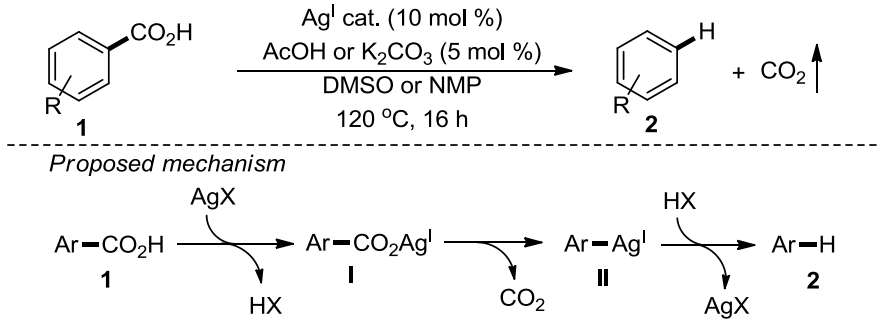



**Scheme 4.** Palladium-catalyzed/promoted decarboxylative protonation of aromatic acids

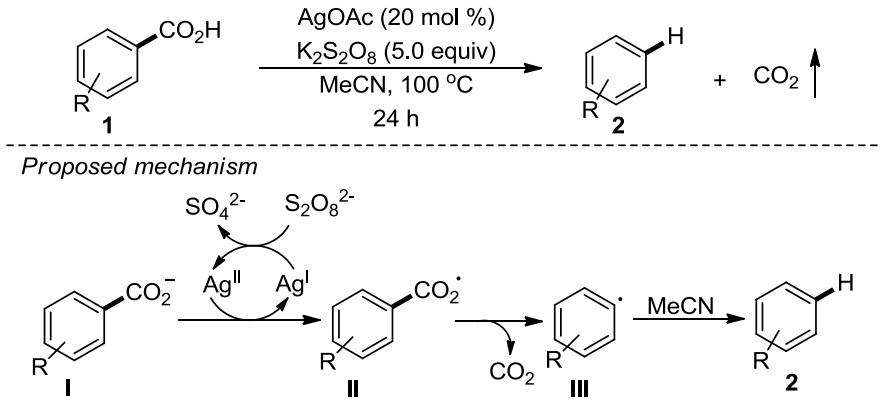
## I.2c. Silver-catalyzed decarboxylative protonation

The Goossen's[22] group and Larrosa's[23] group independently reported the silver(I)-catalyzed decarboxylative protonation of aromatic carboxylic acids and heteroaryl carboxylic acids (Scheme 5). They have observed that using silver as a catalyst the reaction temperature decreases and also the reaction proceed under relatively mild conditions, indicating that the silver(I) salts are more effective in the decarboxylation cross-coupling reactions. This method is applicable to both electron-rich and electron-

deficient benzoic acids. However, *ortho* substitutions on the carboxylic acids are essential for decarboxylative protonation which is a major limitation of this protocol. Mechanistically, first acid-base reaction is occurred between carboxylic acid and silver(I) salt generates silver carboxylate **I**. Subsequently, the silver carboxylate undergoes decarboxylation to yield aryl-silver(I) species **II**. Finally, the aryl-silver(I) species can undergo protonolysis with acids to furnish the product and regenerating the silver(I) catalyst for the next catalytic cycle (Scheme 5).




**Scheme 5.** Silver-catalyzed decarboxylative protonation of aromatic acids




**Scheme 6.** Decarboxylative protonation under radical conditions

A unique system for the decarboxylation protonation via radical pathway was reported by Greaney and co-workers.[24] Although, in the system silver is present as a catalyst but in the presence of a strong single-electron oxidant the reaction proceed via radical pathway (Scheme 6). Mechanistically, the silver(I) catalyst in presence of $K_2S_2O_8$ can generates the carboxyl radical **II** from the carboxylate **I**. Subsequently from the intermediate **II,** the aryl radical **III** is formed via radical decarboxylation process. Finally,

the aryl radical can abstract proton from the solvent to form the desired arene product. Most remarkable point for this method is that the unsubstituted benzoic acid also provided decarboxylative protonation product, which was unsuccessful in other procedures and also *ortho* substituents are not an essential for this transformation.

## I.3. Decarboxylative cross-coupling reactions

Decarboxylative metalation of the C-COOH moiety of a carboxylic acid can generate an intermediate containing a C-metal bond. This organometallic intermediate can couple with electrophiles such as aryl halide or pseudo-halide forming a new C-C bond. Depending on the nature of the C-COOH moiety, a variety of aryl compounds such as biaryls, aryl alkynes, aryl esters, aryl ketones, and others be can produced via decarboxylative cross-couplings.

### I.3.1. Decarboxylative biaryls synthesis

Biaryls are important ubiquitous structural motifs found in various biologically active compounds (Figure 2).[25] Decarboxylative cross-coupling reactions between aromatic carboxylic acids and aryl halides or triflates or tosylates can generate the biaryl compounds. This reaction complements to the typical Suzuki and Stille cross-coupling reactions. In 1966, Nilsson *et al*. first reported biaryl synthesis through decarboxylation process with using stoichiometric copper but this method is not attractive due to drastic reaction conditions.[26]

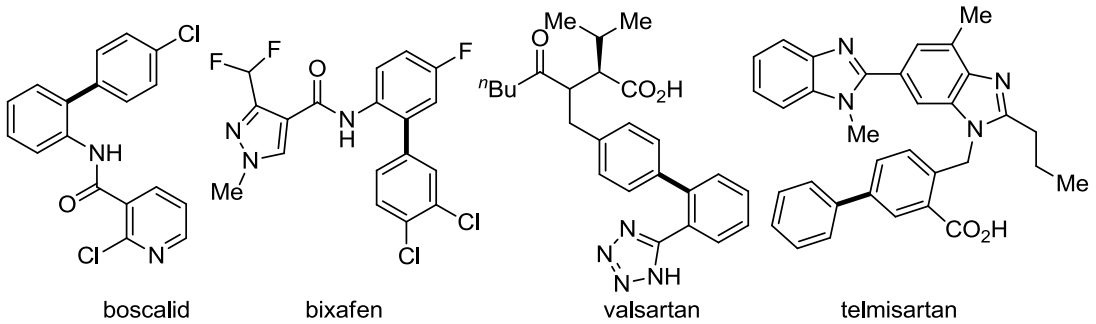
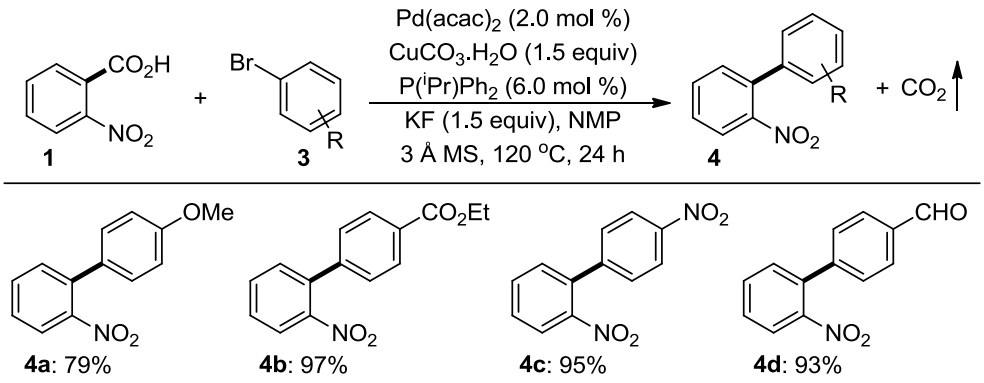



**Figure 2.** Some biologically active biaryl compounds constructed via decarboxylation method

## I.3.1a. Decarboxylative biaryl synthesis using Pd/Cu bimetallic catalyst system

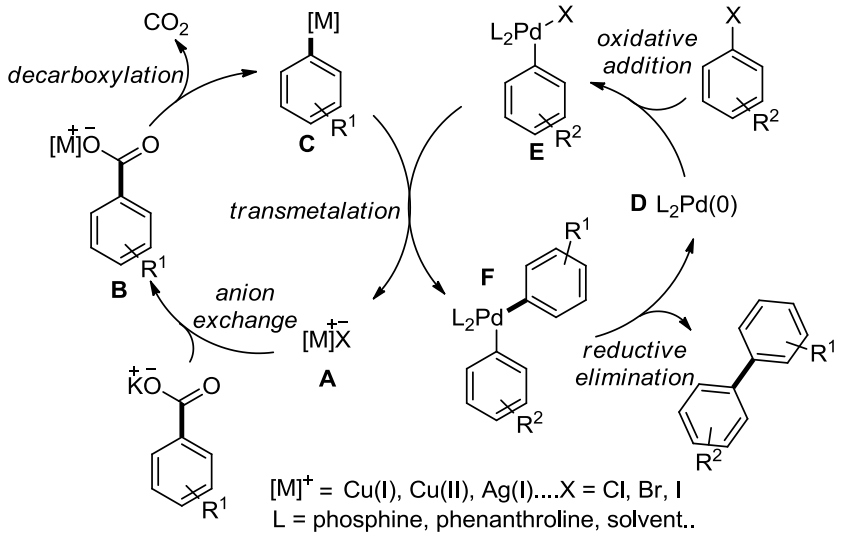
In 2006 Goossen *et al*. first reported a Pd/Cu-catalyzed decarboxylative cross-coupling of aromatic carboxylic acids with aryl halides.[27] In this protocol, 2-nitrobenzoic acids and aryl bromides were stirred in NMP for 24 h at 120 $^{o}$C in the presence of stoichiometric amounts of basic copper carbonate and potassium fluoride, an excess amount of powdered molecular sieves and 2.0 mol % of $Pd(acac)_2/P(^{i}Pr)Ph_2$ catalyst. A ArC(O)OCuF salts were generated which undergo decarboxylation to form a aryl-copper-fluoride species. Finally, the aryl copper species can be coupled with various types of aryl bromides by the palladium co-catalyst (Scheme 7). Subsequently, a second-generation catalytic system has also been developed by Goossen's group consisting of 10 mol % of CuBr/phenanthroline and 3.0 mol % of $PdBr_2$. This method is more broadly applicable to a wide range of substrate with respect to carboxylates and aryl halides providing excellent yields of the decarboxylative cross-coupling product.[28]




**Scheme 7.** Palladium catalyzed decarboxylative biaryl synthesis

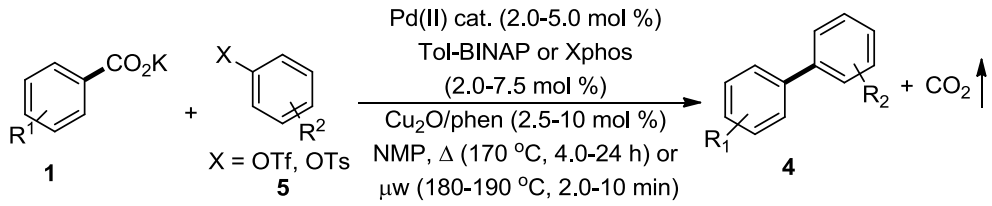
The proposed mechanism for the decarboxylative biaryl synthesis using bimetallic catalyst system is outlined in Scheme 8. The reaction starts with the extrusion of $CO_2$ from a metal carboxylate **B**, which is generated by salt exchange from a potassium salt of carboxylic acid and a copper salt **A**. The resulting aryl-copper species **C** transfers its aryl group to an aryl-palladium(II) complex **E** which is generated by oxidative addition of palladium co-catalyst **D** to aryl halide giving rise to a biaryl-palladium species **F** via

transmetalation process. The catalytic cycle for the palladium is completed by reductive elimination with the formation of biaryl product and regenerating the initial palladium(0) catalyst **D** for the subsequent runs.



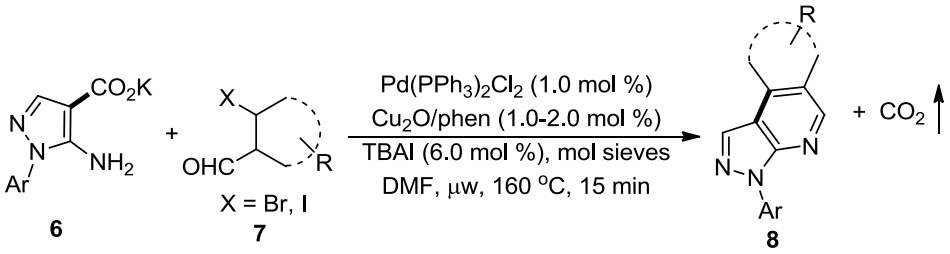

**Scheme 8.** Mechanism for decarboxylative biaryl synthesis using bimetallic system

Subsequently the Goossen's group has optimized the catalysts system and ligands to expand the scope. As a result, they were able to extend the above cross-coupling reaction to triflates[29] and also less expensive tosylates[30] (Scheme 9). It has been observed that the chloride or bromide anion generated in the reaction can inhibits the Cu-catalyzed decarboxylation process.[28] Therefore, when aryl triflates were used, the substrate scope was extended to some less activated aromatic carboxylates carrying no *ortho*-substituent. The reaction can be performed either using conventional heating (170 $^{o}$C, 24 h) or microwave heating (190 $^{o}$C, 5-10 min).[31] The microwave method is superior than conventional heating protocol and given higher yield particularly when deactivated carboxylates were used in the reaction.



**Scheme 9.** Decarboxylative biaryl synthesis using aryl triflates or aryl tosylates

In 2013, the Batra group has successfully developed an interesting protocol for the synthesis of a variety of fused-heterocyclic via intermolecular cascade imine formation/decarboxylative coupling of potassium 5-amino-1-phenyl-1*H*-pyrazole-4-carboxylates and 3-amino-thiophene-2-carboxylate with 2-haloarylaldehydes (Scheme 10).[32]



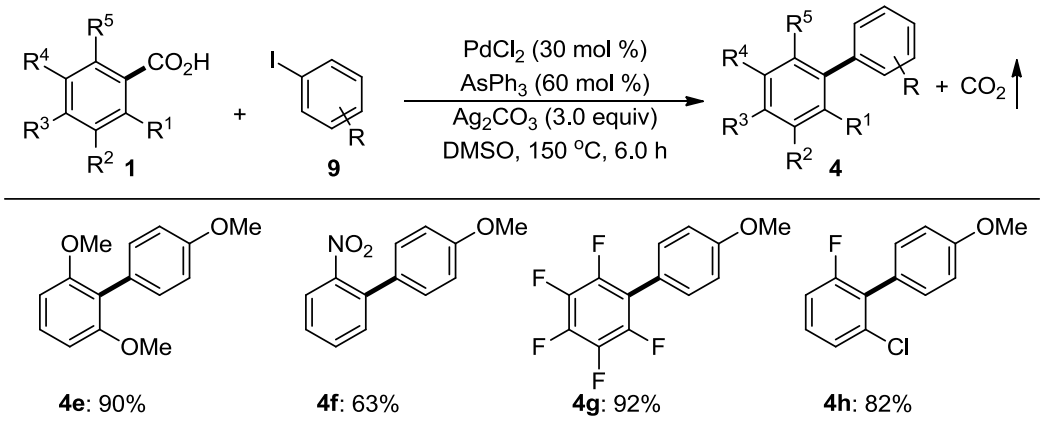

**Scheme 10.** Synthesis of heterocycles via cascade imination/decarboxylative coupling

## I.3.1b. Decarboxylative biaryl synthesis using Pd/Ag bimetallic catalyst system

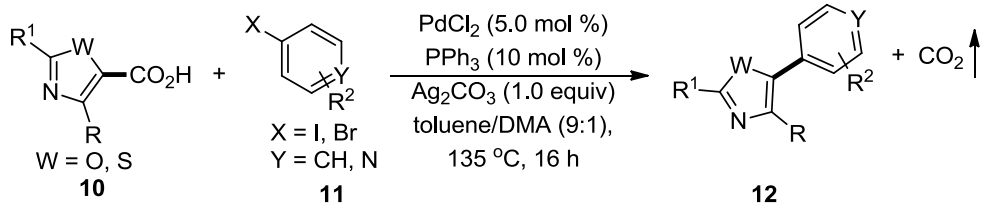
Becht *et al*. first reported a Pd(II)-catalyzed decarboxylative biaryl synthesis between aromatic carboxylic acids and aryl iodides[33] or diaryl-iodonium salts[34] in the presence of silver. In the reaction 30 mol % of palladium chloride, 60 mol % of triphenylarsine ligand and stoichiometric amount of silver carbonate was used in DMSO (Scheme 11). In 2009, a similar type of reaction was reported by the Wu group using a $PdCl_2$/BINAP catalyst system and $Ag_2CO_3$ as a base in the reaction. A good to excellent yield were achieved for *ortho*-substituted aromatic carboxylic acids.[35]

In 2010, the Greaney group reported a decarboxylative cross-coupling reaction of substituted oxazole- or thiazole-5-carboxylic acids with aryl bromides and iodides (Scheme 12).[36] They have used a Pd/Ag bimetallic catalyst system for this transformation. The reaction is interesting due to prevalence of the products in medicinal and agrochemistry.[37] However, most of the cases a stoichiometric amount of Ag salt is required in Pd/Ag bimetallic system. This is due to the formation of insoluble silver halides in the reaction medium which prevents the regeneration of silver catalyst in the

catalytic cycle for subsequent runs. To overcome this problem, the Goossen's group first successfully developed a decarboxylative cross-coupling reaction between arene carboxylates and aryl triflates, where both Pd- and Ag-salts were used in catalytic amount.[38]




**Scheme 11.** Decarboxylative biaryl synthesis using Ag/Pd bimetallic system



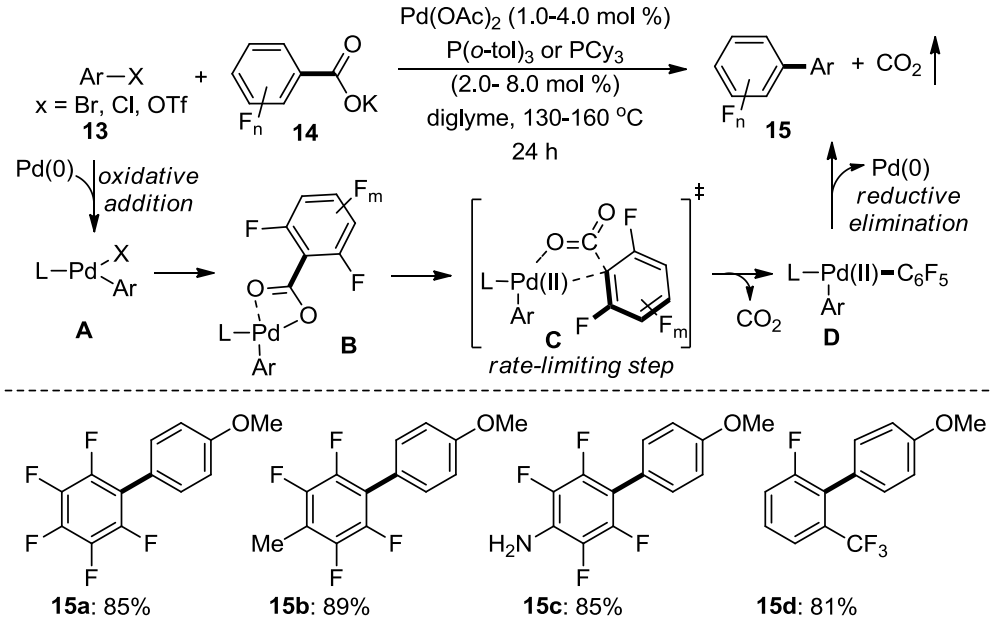

**Scheme 12.** Decarboxylative (het)arylation of thiazoles and oxazoles using Ag/Pd system

## I.3.1c. Palladium-catalyzed decarboxylative biaryl synthesis

Without other metal complexes, palladium complexes can also participate in the decarboxylative cross-coupling reaction of some particularly activated carboxylates. The Steglich group first successfully described such reaction in their total synthesis of lamellarin L via intramolecular fashion.[39] Subsequently, Forgione and Bilodeau *et al*. successfully reported an intermolecular decarboxylative cross-coupling reaction catalyzed by palladium only using a number of heteroaromatic carboxylic acids with aryl halides.[40] Shang *et al*. showed polyfluorinated benzoic acids can also undergo Pd-catalyzed decarboxylative cross coupling with aryl bromides, chlorides, and even triflates.[41] The presence of fluorine substitution at the *ortho* position of the carboxylates

is crucial to the reaction outcome. The presence of fluorine group at the *ortho* position may facilitate the carbon dioxide extrusion (Scheme 13).

Based on DFT calculations, they showed that the palladium-mediated decarboxylation step is the rate-determining step in the catalytic cycle. Mechanistically, first active Pd(0) catalyst is generated from the combination of Pd(II) and phosphine ligand which reacts with aryl halides or aryl triflates via oxidative addition to generate an aryl-Pd(II) intermediate **A**. Then aryl-Pd(II) intermediate **A** reacts with the carboxylate forming intermediate **B**. From the intermediate **B** a bisarylated-Pd(II) complex **D** is formed via four member cyclic transition state followed by decarboxylation. Finally, reductive elimination furnish the desired C-C coupled product and re-generate the Pd(0) catalyst for subsequent catalytic cycles (Scheme 13).

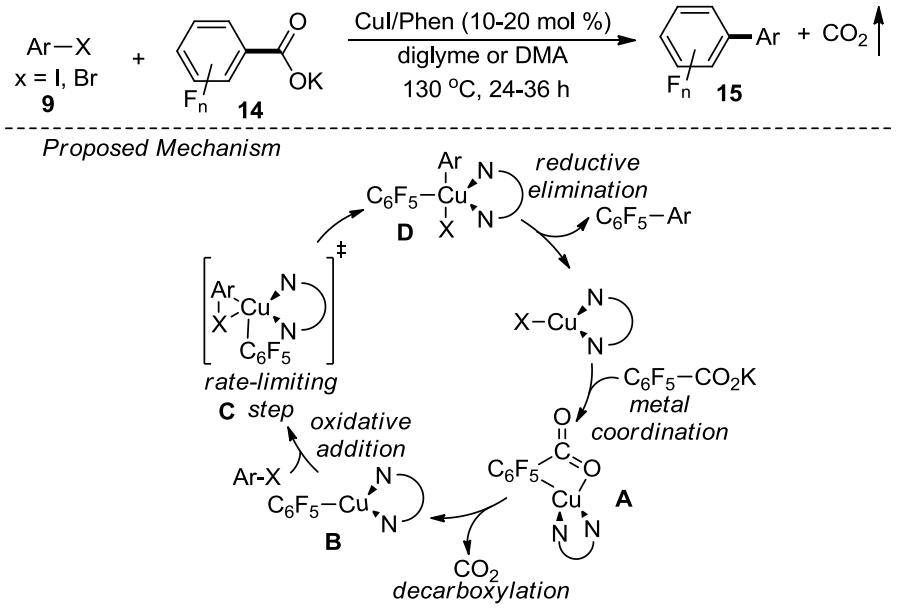



**Scheme 13.** Palladium-catalyzed decarboxylative arylation

## I.3.1d. Copper-catalyzed decarboxylative biaryl synthesis

In 2009, Shang *et al*. first reported a monometallic copper-catalyzed decarboxylative cross coupling of potassium polyfluorobenzoates with aryl bromides and iodides affording fluorinated biaryls (Scheme 14).[42] Based on DFT calculations, they have proposed the mechanism in which the decarboxylation occurs from the Cu(I) complex of

the polyfluorinated aromatic acid, generating an aryl-Cu(I) intermediate. The aryl-Cu(I) intermediate can reacts with the aryl halide through oxidative addition to form a bis-arylated Cu(III) complex. Finally, the biaryl product is produced from bis-arylated Cu(III) complex via reductive elimination and re-generating the Cu(I) catalyst for next catalytic cycle. In contrast to palladium-catalyzed decarboxylative couplings, here the oxidative addition step is the rate-determining step in the catalytic cycle (Scheme 14).



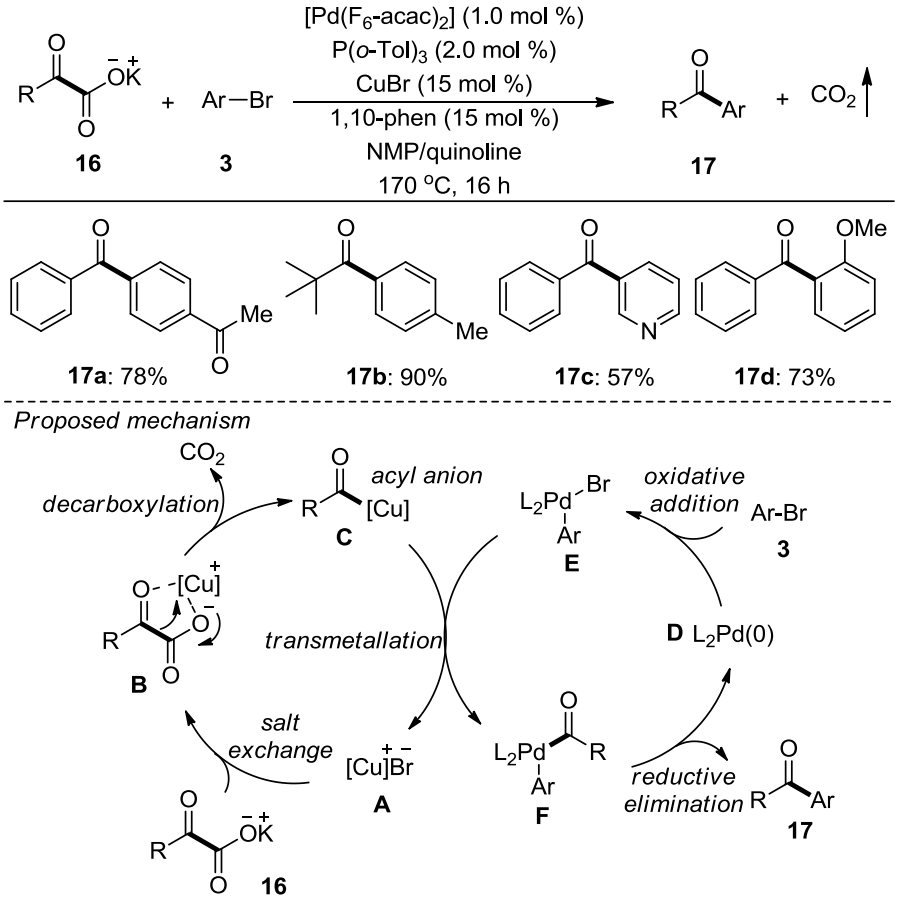

**Scheme 14.** Cu-catalyzed decarboxylative coupling of polyfluorobenzoates with aryl halides

## I.3.2. Decarboxylative ketone synthesis

Aryl ketones are important structural motifs in biologically active compounds and functional materials.[43] In 2008, Goossen and coworkers have successfully developed a Cu/Pd-catalyzed decarboxylative coupling of *α*-oxocarboxylic acids with aryl halides or pseudo-halides to give aryl ketones (Scheme 15).[44] This transformation is mainly interesting due to the generation of acyl anion equivalent which is reverse polarity of the keto group and the acyl anion equivalents coupled with carbon electrophiles.

Initially, the potassium α-oxocarboxylate reacts with the copper(I) complex **A** by ligand exchange to form the copper-carboxylate **B**. The copper-carboxylate **B** afforded

the acyl-copper species **C** via decarboxylation. On the other hand, the aryl-palladium(II) species **E**, which is formed through the oxidative addition of the palladium(0) catalyst **D** to the aryl halide. Then from the species **C** transfers its acyl moiety to the aryl-palladium(II) species **E** afforded the acyl-aryl-palladium(II) intermediate **F** via transmetalation and the copper(I) complex is released in the copper catalytic cycle, Finally, aryl ketone is formed via reductive elimination and regenerating the palladium(0) catalyst **D** for next catalytic cycles (Scheme 15).

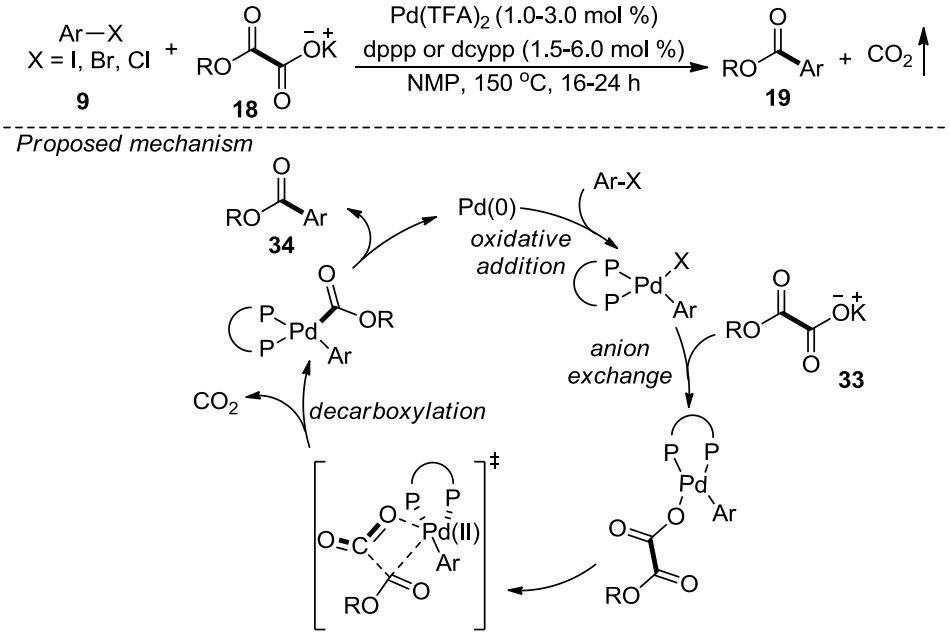



**Scheme 15.** Cu/Pd-catalyzed decarboxylative ketone synthesis

## I.3.3. Decarboxylative esters synthesis

Oxalic acid monoesters are another important class of carboxylates that can also be cross-coupled with aryl halides using monometallic palladium catalyst via decarboxylation process producing the corresponding arenecarboxylate esters (Scheme 16).[45] This

reaction is a distinct class of cross-coupling with an acyl anion species which is generated via decarboxylation of oxalic acid monoesters. In the reaction copper salt is not required for the decarboxylation but bulky and electron-rich bidentate phosphine ligands favor for the reaction. Theoretical calculation showed that decarboxylation via a five-coordinated Pd(II) transition state is the rate-limiting step in the catalytic cycle.



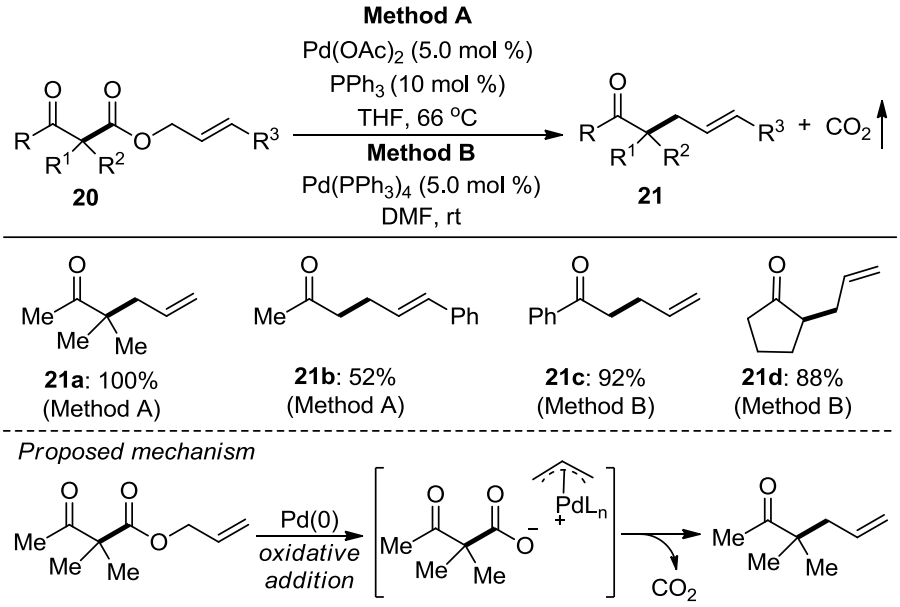

**Scheme 16.** Decarboxylative ester synthesis

## I.4. Decarboxylative allylation

Decarboxylative allylation reaction is a powerful synthetic approach in organic synthesis.[46] In the decarboxylative allylation reactions, allyl electrophiles coupled with nucleophiles formed via decarboxylation in a chemo-, regio-, and stereo-selective manner. In the presence of a base, *β*-ketocarboxylic acid allyl esters undergo decarboxylation at higher temperature (170 °C) to furnish *γ,δ*-unsaturated alkyl ketones. This reaction occurred via the thermal rearrangement of the *β*-keto allyl ester, followed by decarboxylation and then an anion-assisted Claisen rearrangement.[47] In 1980, the Saegusa[48] and Tsuji[49] group first independently showed that palladium catalysts can promote this decarboxylative process under very mild conditions. In Tsuji's method, they have used allyl esters of acetoacetic acid in the presence of catalytic amount of $Pd(OAc)_2$

and $PPh_3$ providing $\gamma,\delta$-unsaturated methyl ketones in high yield (Scheme 17, Method A). In Saegusa's method, they used a variety of acyclic and cyclic keto-esters in the presence of 5.0 mol % of $Pd(PPh_3)_4$ as the catalyst which undergo decarboxylative coupling providing the allylated product with excellent yields (Scheme 17, Method B).

Mechanistically, palladium(0) undergoes an oxidative addition to the allyl ester to form a $\pi$-allyl-Pd complex and corresponding carboxylate. Then subsequent decarboxylation occurs from the carboxylate, generating the incipient carbanion which is resonance stabilized by the adjacent keto group. Finally, incipient anion acts as a nucleophile coupled with the electrophile, $\pi$-allyl-Pd complex to yield the desired allylation product via reductive elimination and regenerating Pd(0) catalyst for next catalytic cycles (Scheme 17).

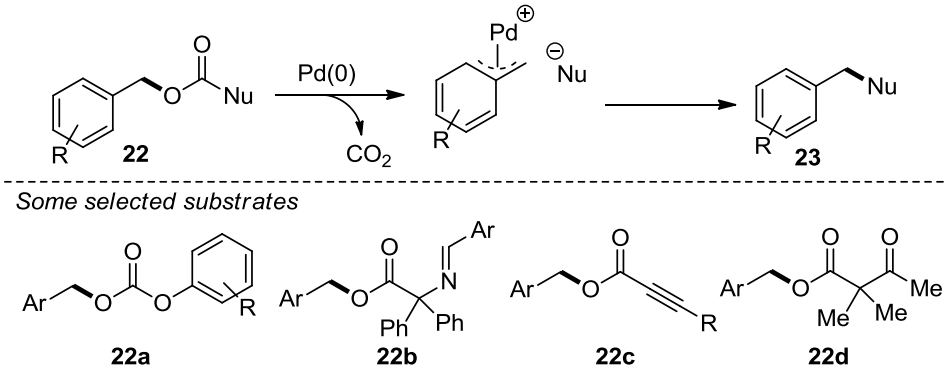



**Scheme 17.** Decarboxylative allylation reaction

Over the last decade, different types of decarboxylative allylation reaction have been developed and it has wide application in organic synthesis.[50] Detailed discussion is in **Chapter II**.

## I.5. Decarboxylative benzylation

Decarboxylative benzylation reaction is also a powerful synthetic approach for the C-C and C-hetero bond formation in organic synthesis.[51] In intramolecular decarboxylative benzylation reactions, initially, a stabilized $\pi$-benzyl-Pd intermediate is formed through oxidative addition with palladium which act as an electrophile. Subsequently, it cross-couples with the nucleophile, that is generated through decarboxylation (Scheme 18).



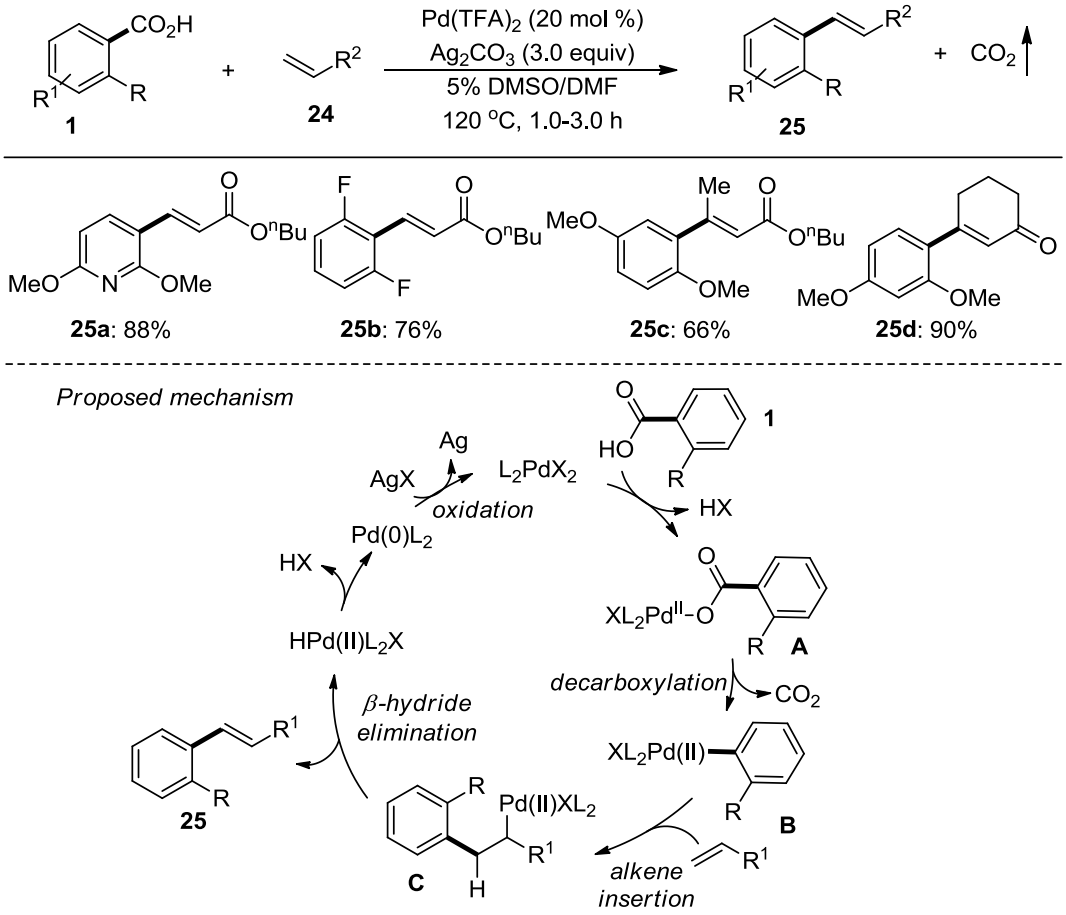

**Scheme 18.** Decarboxylative benzylation reactions

## I.6. Oxidative decarboxylative cross-coupling reactions

The reactions discussed earlier, the carboxylic acids serve as a source of carbon nucleophile which further couples with a carbon electrophile under metal catalysis. The decarboxylative cross-coupling can also takes place with a nucleophilic coupling partner by the addition of stoichiometric amounts of an oxidant. Examples of such oxidative transformations are decarboxylative Heck reactions or direct decarboxylative C-H functionalization.

### I.6.1. Decarboxylative Heck reaction

In 2002, Myers and coworkers have developed a novel palladium-catalyzed decarboxylative olefination reaction of arene carboxylic acids with olefins (Scheme 19).[52] The methodology is only applicable to heteroaromatic 2-carboxylic acids or *ortho* substituted aromatic carboxylic acids providing variety of vinylarenes. In the reaction, a stoichiometric amount of $Ag_2CO_3$ was used as an oxidant along with a catalytic amount of $Pd(TFA)_2$ in 5% DMSO-DMF.



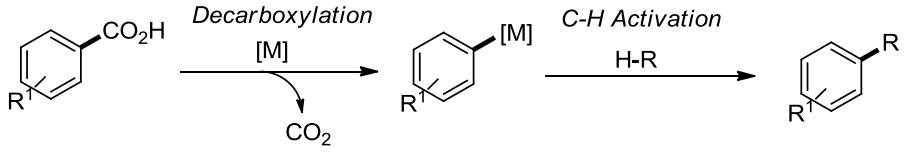

**Scheme 19.** Decarboxylative Heck reaction

Based on NMR studies and X-ray crystallographic analysis,[53] they showed that Pd(II)-mediated decarboxylation creates the first step of the catalytic cycle generating an aryl-palladium(II) intermediate **B** from a palladium(II) carboxylate species **A**. In the traditional Heck reaction, the same intermediate is formed via the oxidative addition of palladium(0) to an aryl halide. The subsequent elementary steps such as alkene insertion, internal migration and finally *β*-hydride elimination are common in both processes to produce aryl alkene product. However, in oxidative or decarboxylative Heck reaction, an additional step is required to regenerate the Pd(II) catalyst in the catalytic cycle from Pd(0) via oxidation. In this method $Ag_2CO_3$ was used for re-oxidation of the catalyst for the catalytic turnover (Scheme 19).

Over the past decade, a remarkable advancement has been achieved for different kinds of decarboxylative Heck reaction and it has wide application in organic synthesis. Details we discussed in **Chapter III**.

## I.6.2. Decarboxylative C-H functionalization

The organometallic species which is generated via a decarboxylative metalation step has been coupled with metal-catalyzed C-H bond of other coupling partner to form a new C-C bond. This method merges modern C-H functionalization processes with state-of-the-art decarboxylation protocols, giving birth to a new attractive field called decarboxylative C-H functionalization.[12]



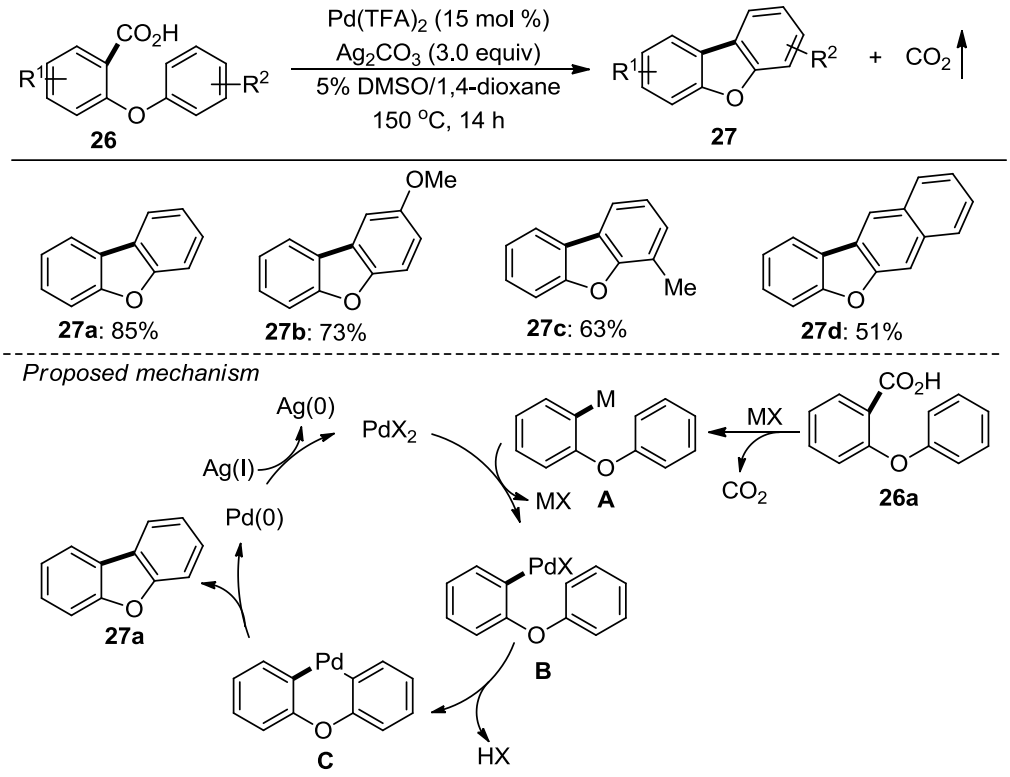

**Scheme 20.** Decarboxylative C-H functionalization

Aromatic compounds, such as anilines, phenols, pyridines, thiophenes, and also heteroaromatic compounds, represent a highly important class of organic compounds. The synthetic transformations of this compounds using transition metal-catalyzed C-H functionalization via decarboxylation can provide a vast amount of structurally diverse molecules. This cross-coupling is feasible between (hetero)arenes and carboxylic acids with or without the assistance of a directing group.

## I.6.2a. Decarboxylative C-H arylation

In their seminal work in 2008, Crabtree and coworkers first reported the direct decarboxylative C-H arylation of simple arene.[54] Anisole and 2,6-dimethoxybenzoic acid were utilized as the coupling partners affording a mixture of *meta*- and *para*-arylated products in 3:1 ratio. Besides the desired coupling products, large quantities of decarboxylative protonation product, 1,3-dimethoxybenzene from 2,6-dimethoxybenzoic acid was formed.

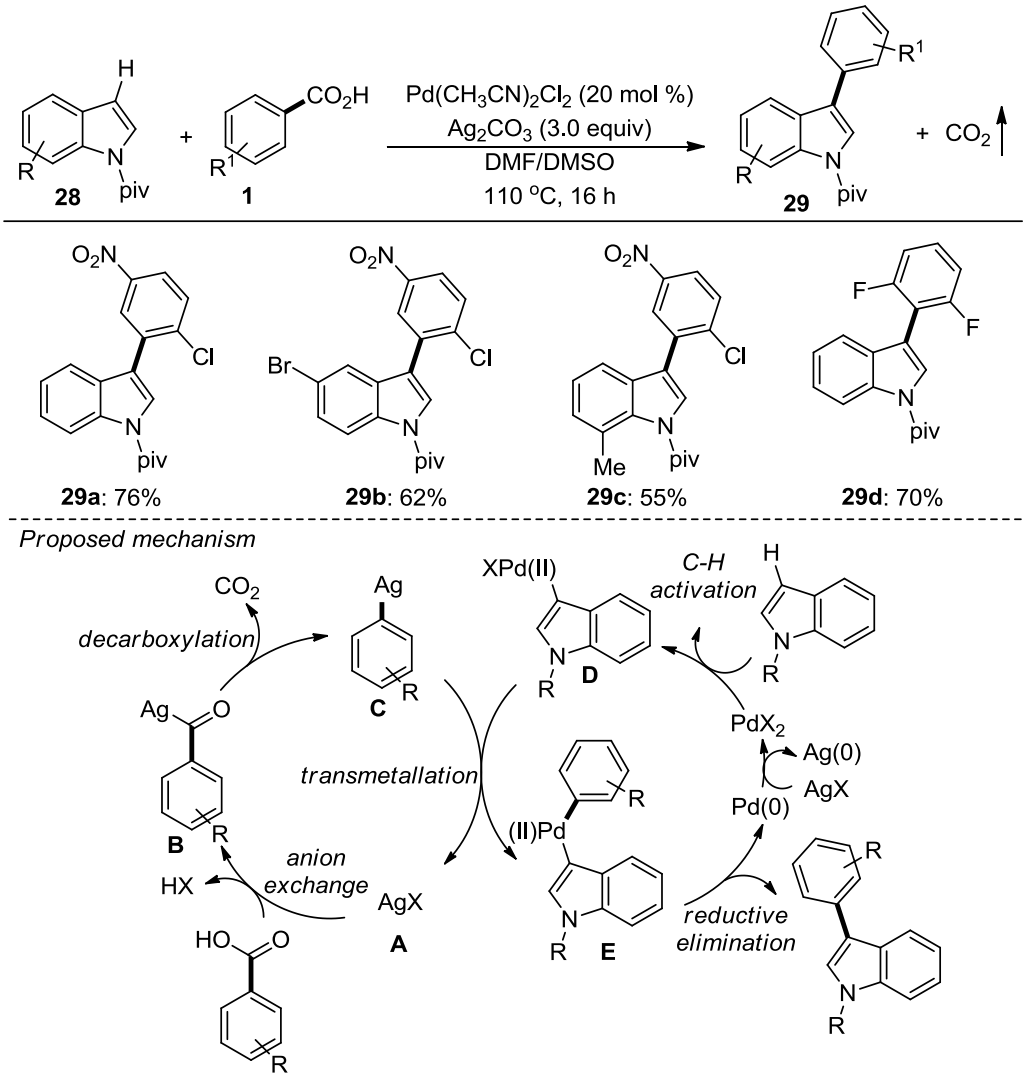
Subsequently, the Glorius group have developed a highly chemo- and regioselective, palladium(II)-catalyzed intramolecular direct arylation of ether linked benzoic acids by tandem decarboxylative C-H bond activation to produce the dibenzofuran moiety (Scheme 21).[55] They showed that Ag salts not only assist the decarboxylation step, but also act as oxidant to the palladium for catalytic turnover. Mechanistically, silver-mediated decarboxylation of 2-phenoxybenzoic acid afforded silver-aryl species **A** followed by transmetalation with a Pd(II) complex results in the formation of an aryl-palladium (II) intermediate **B**, which can undergo intramolecular C-H activation to generate palladacycle intermediate **C**. Finally, the product dibenzofuran is formed via reductive elimination and generating the catalyst Pd(II) from Pd(0) by silver(I) carbonate for next catalytic cycle (Scheme 21).




**Scheme 21.** Pd-catalyzed intramolecular decarboxylative arylation reaction

For functionalization of the heteroaromatic C-H bond, the Larrosa group have successfully established a Pd/Ag bimetallic catalytic system for direct decarboxylative C3-H arylation of indoles using benzoic acids as the aryl donors (Scheme 22).[56] The

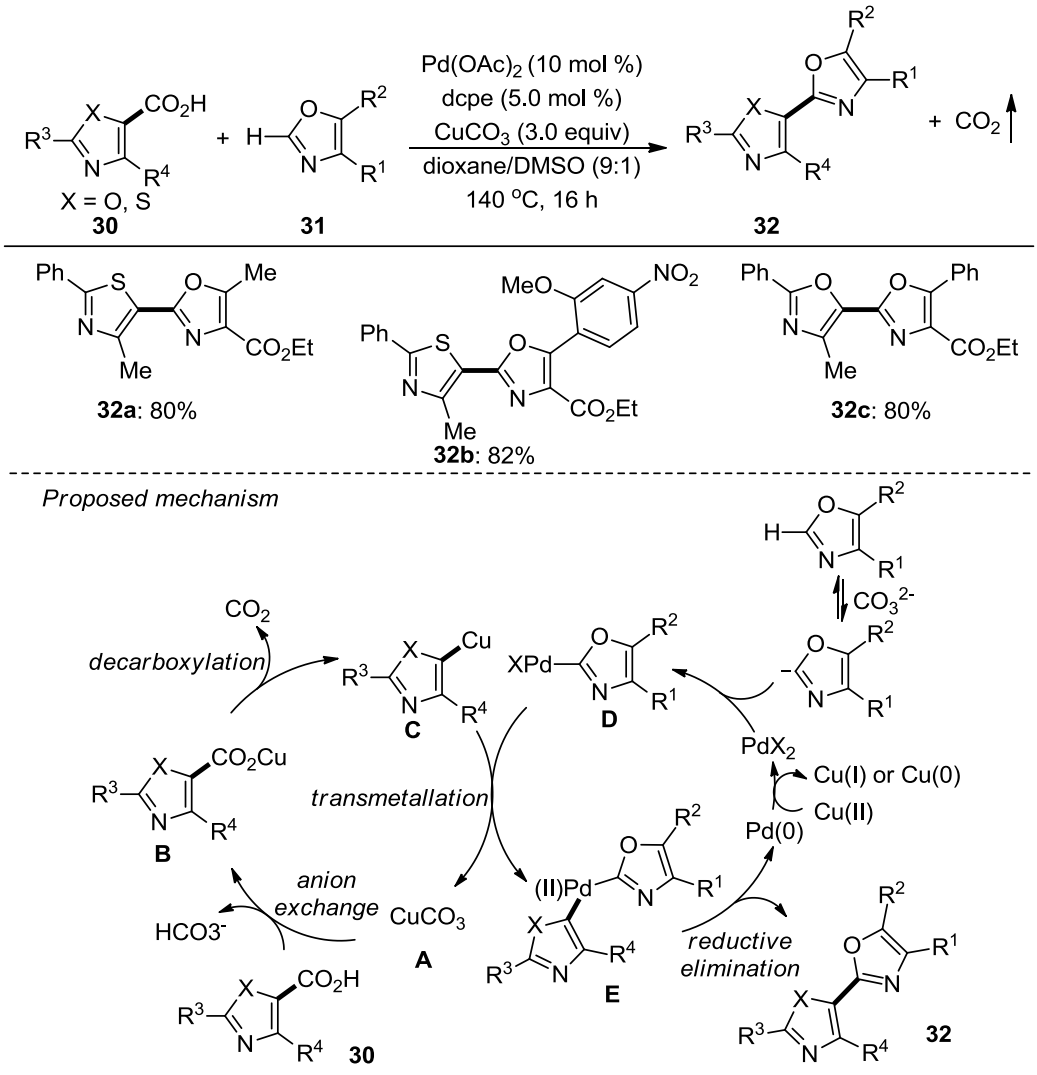
reaction occurred in the presence of $Pd(MeCN)_2Cl_2$ as a catalyst and $Ag_2CO_3$ as an oxidant. It has been observed that the reactions showed excellent regioselectivity only given the C3 arylated products of the *N*-protected indole.




**Scheme 22.** Pd-catalyzed decarboxylative C3-H arylation of indoles

To understand the reaction mechanism, they performed several control experiments and reveals that the silver is responsible for the decarboxylation process, and palladium is responsible for C-H activation process in the reaction where both metals are necessary for the C-H arylation. Mechanistically, palladium activated the C3-H bond of indole generates an aryl-palladium species **D**, which reacts with an aryl-silver species **C** derived from silver-mediated decarboxylation of arene carboxylic acid to form a diaryl-

palladium complex **E** via transmetalation process. From the diaryl-palladium complex **E**, the biaryl product is furnished through reductive elimination. The generated Pd(0) species can be oxidized into Pd(II) species by $Ag_2CO_3$ for next cycle (Scheme 22).

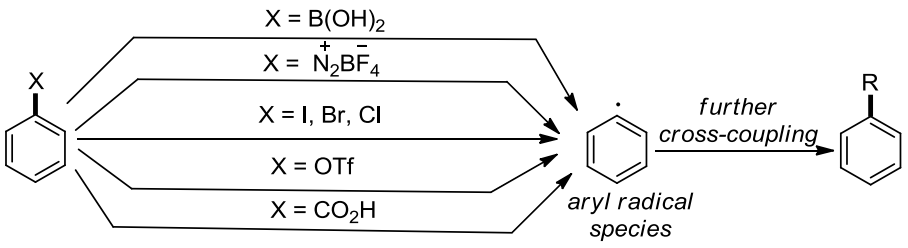



**Scheme 23.** Palladium-catalyzed decarboxylative C-H hetero-arylation of azoles

In 2010, Greaney and co-workers developed a Cu/Pd catalytic system for the decarboxylative C-H hetero-arylation reaction of azoles moiety for the synthesis of biologically and pharmaceutically important oxazoles, thiazoles, and imidazoles using heteroaromatic acids (Scheme 23).[57] The reaction is catalyzed by $Pd(OAc)_2$ in the presence of stoichiometric amounts of copper salts and sterically hindered bidentate bis(dicyclohexylphosphino)ethane(dcpe) ligand in dioxane/DMSO. Mechanistically,

copper-mediated decarboxylation of the heteroaromatic acid generates an aryl-copper species **C**. On the other hand, the acidic C-H bond of the oxazole undergoes deprotonation in the presence of base $CO_3^{-2}$, generating an aryl-palladium(II) species **D**, which then reacts with the aryl-copper species to give a diaryl-palladium(II) intermediate **E** through transmetalation process. Finally, reductive elimination affords the hetero-biaryl product and Pd(0) catalyst, which is oxidized to Pd(II) by Cu(II) to complete the catalytic turnover (Scheme 23).

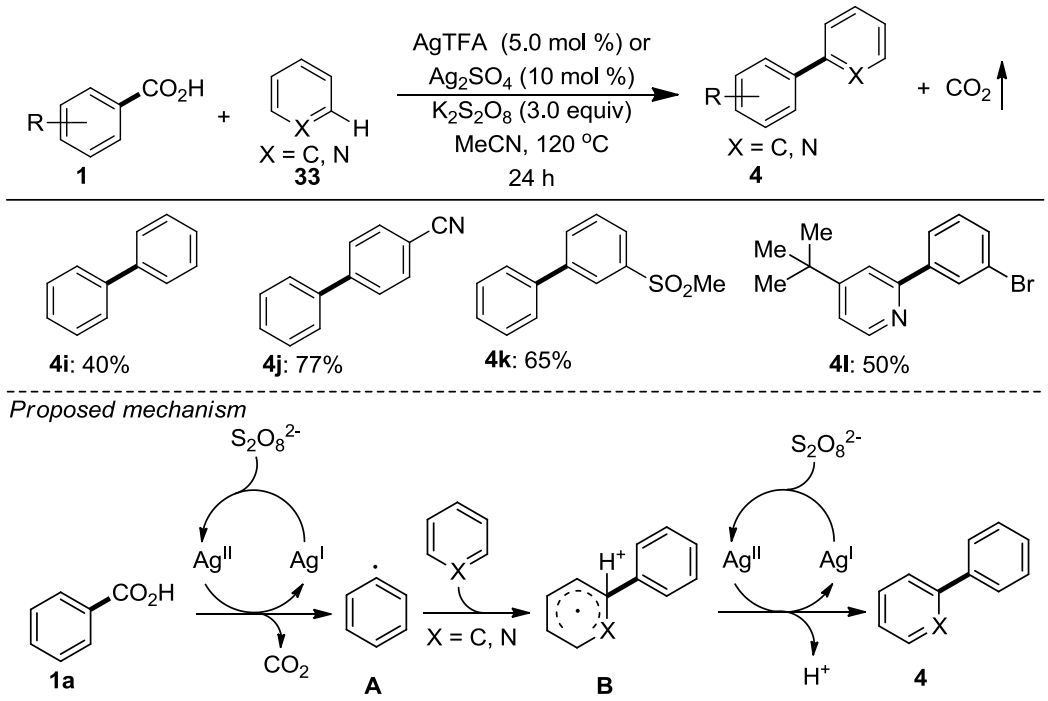
Aryl radicals are useful synthetic intermediates in organic transformation.[58] Due to their high reactivity, aryl radicals can be generate only from limited functional groups such as aryl boronic acids,[59] aryl diazonium salts[60] and also aryl halides.[61] But these methods are not practical due to less availability, unstable and expensive starting materials. Very recently, the Li group reported a simple and efficient method for the generation of aryl radical from less expensive aryl triflates (Scheme 24).[62] Recently, taking the advantages of carboxylic acids in the decarboxylative cross-coupling reaction, Su and co-workers showed the generation of aryl radical species from simple arene carboxylic acids via radical decarboxylative process.[63] The Glorius group also reported visible light mediated decarboxylation of aromatic carboxylic acids to provide aryl radical species.[64] In the reaction, aryl radical species is formed via the extrusion of carbon dioxide which is then coupled with arenes via Minisci type radical reaction (Scheme 25).[65]




**Scheme 24.** Generation of aryl radical from different methods

For the generation of aryl radical from the corresponding benzoic acid derivatives, the Su group has adopted catalytic amount of inexpensive silver salt and stoichiometric amount of $K_2S_2O_8$ as a catalyst and oxidant respectively.[63] Mechanistically, the silver(I)

salt is oxidized to a silver(II) in the presence of persulfate anion. Then the silver(II) species oxidizes the aromatic carboxylic acids leading to decarboxylation and producing an aryl radical species **A**. Subsequently, the aryl radical combined with benzene or pyridine to generate the cyclohexadienyl radical intermediate **B**. Finally, **B** is oxidized by the silver(II) species to re-aromatize forming the desired arylated product **4** (Scheme 25).

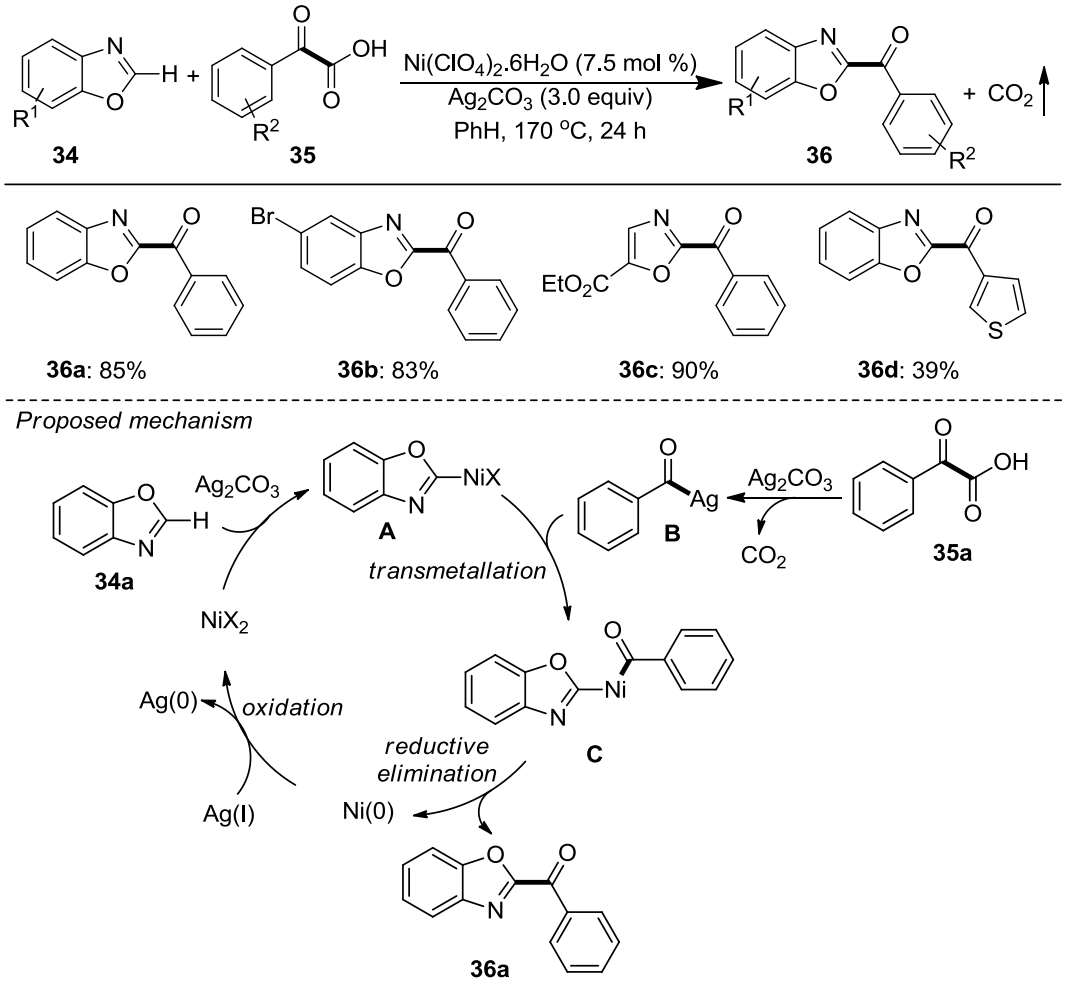



**Scheme 25.** Silver-catalyzed decarboxylative C-H arylation of simple arenes

## I.6.2b. Decarboxylative C-H acylation

The *α*-ketocarboxylic acids have been explored for the transition metal-catalyzed decarboxylative C-H bond functionalization reactions. In this case, the *α*-ketocarboxylic acids act as the acyl donor towards synthesis of ketones. Recently, Zhang group reported a Cu-catalyzed decarboxylative C3-H acylation of indoles.[69] Ge and co-workers have successfully developed a Ni-catalyzed acylation reaction of azoles with *α*-ketocarboxylic acids (Scheme 26).[67] The proposed mechanism is similar to the decarboxylative C-H bond (hetero)arylation reactions, involving Ni-catalyzed C-H bond activation and Ag-mediated decarboxylation process. In the catalytic cycle, first nickelation of azole is occurred in the presence of $Ag_2CO_3$ generating an aryl-Ni (II) intermediate **A**. Then

transmetalation between the intermediate **A** and the acyl-Ag species **B**, which is formed by silver mediated decarboxylation of $\alpha$-ketocarboxylic acid, generating an acyl-aryl-Ni (II) species **C**. Finally, the desired product ketone is formed via reductive elimination of species **C**, and Ni(0) catalyst is generated in the catalytic cycle, which could be re-oxidized to the divalent Ni(II) species by a Ag(I) species for catalytic turnover (Scheme 26).



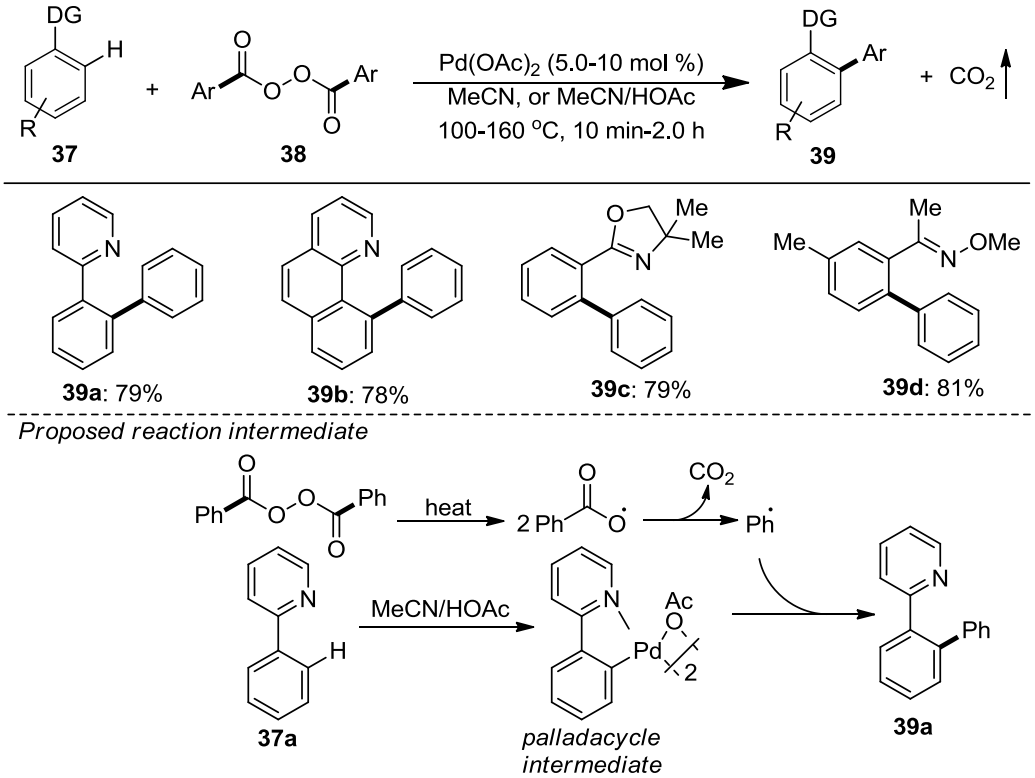

**Scheme 26.** Ni-catalyzed decarboxylative C-H acylation

## I.6.2c. Directed decarboxylative C-H arylation

Functional groups containing heteroatoms, such as N, O, and S, are generally used as directing groups to promote the transition metal catalyzed inert C-H bond functionalization. The directing groups can locate the position of the metals in the substrate for the chemo- and/or regioselective C-H functionalization. On the other hand,

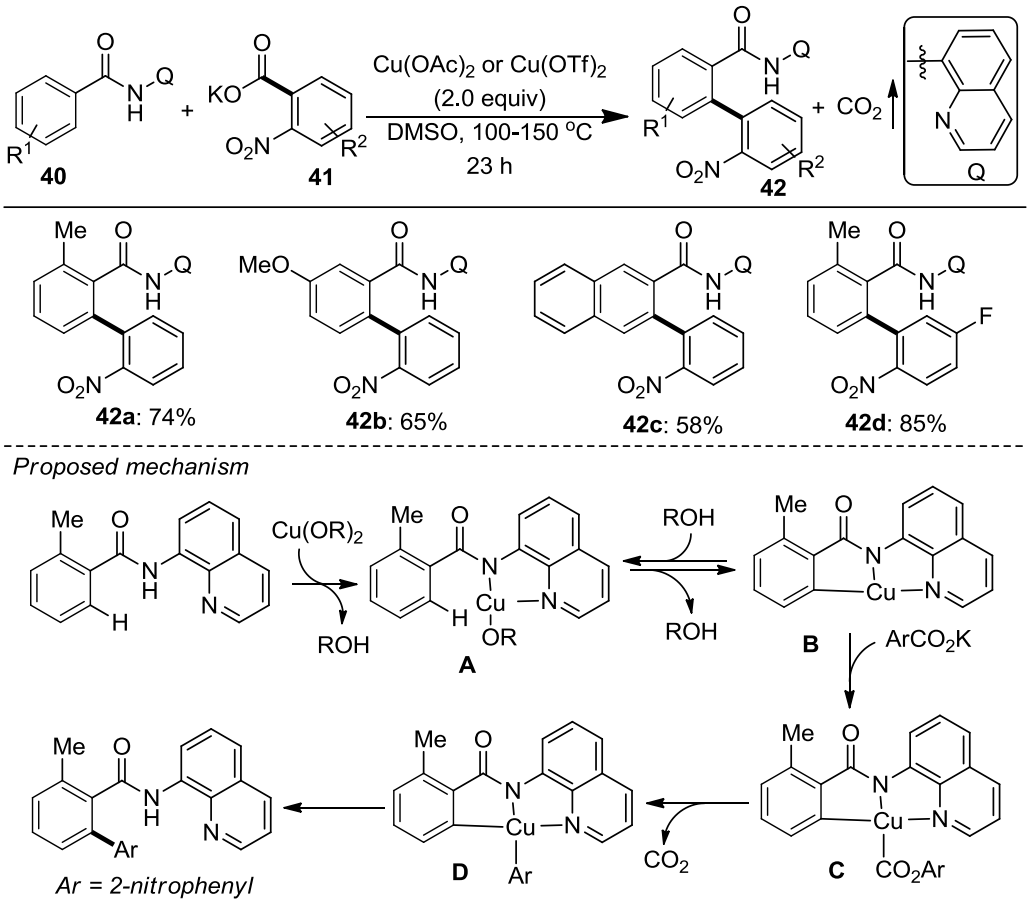
directing groups can also stabilizes the organometallic species generated by C-H bond cleavage, such as palladacycle and rhodacycle intermediate, which can take part for further transformations to furnish the desired products. Consequently, variety of directing groups has been successfully explored for the decarboxylative C-H bond cross-couplings.

In this vein, Yu and coworkers demonstrated chelation-assisted decarboxylative $sp^2$ C-H arylation using aryl acyl-peroxides (Scheme 27).[68] In the reaction, it has been observed that various types of *N*-containing directing groups such as pyridine, oxazole, and also oxime are compatible in the reaction and exhibit good reactivity and selectivity toward the Pd-catalyzed decarboxylative $sp^2$ C-H arylation reactions. To understand the reaction mechanism, they have done several control experiments and proposed the reaction intermediate in scheme 27. The pyridine-assisted cyclopalladation of Pd(II) via electrophilic palladation generates 5-membered palladacycle dimer intermediate which undergoes oxidative addition with the aryl radical which is generated by thermal decomposition of aryl acyl-peroxides to afford the biaryl product.




**Scheme 27.** Chelation assisted Pd(II)-catalyzed decarboxylative C-H arylation

Very recently, the Miura group has developed a copper-mediated decarboxylative C-H arylation of benzamides with *ortho*-nitrobenzoic acids by 8-aminoquinoline directed (Scheme 28).[69] In the reaction, the 8-aminoquinoline moiety in the substrate is crucial for the reaction outcome and the N-H bond in the amide is also essential. Other bidentate directing groups did not work under the reaction conditions. Mechanistically, they have shown that an initial deprotonation of relatively acidic NH in the substrate generates the *N*,*N*-bidentate chelated complex **A**. Subsequent reversible C-H bond cleavages forms a five-membered metallacycle intermediate **B**. The copper(III) intermediate **C** is then generated from the intermediate **B** via disproportionation with another copper(II) and carboxylate species. The aryl-copper species **D** is generated from the intermediate **C** via copper-mediated decarboxylation. Finally, the corresponding arylated product is formed by reductive elimination (Scheme 28).




**Scheme 28.** Chelation assisted Cu(II)-mediated decarboxylative C-H arylation

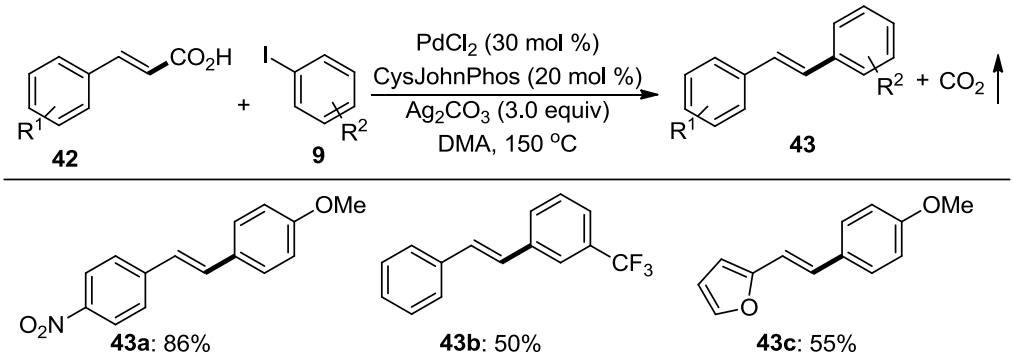
## I.6.2d. Directed decarboxylative C-H acylation

(Details we discussed in **Chapter IV**)

## I.7. Decarboxylative cross-couplings of cinnamic acids

Over the last few years, an efficient and versatile method has been development particularly using cinnamic acids as a coupling partner in decarboxylative cross-couplings.[70] Apart from the transition metal catalysts, cinnamic acids are also found to undergo decarboxylation under metal-free conditions and photoredox conditions.[70,71]

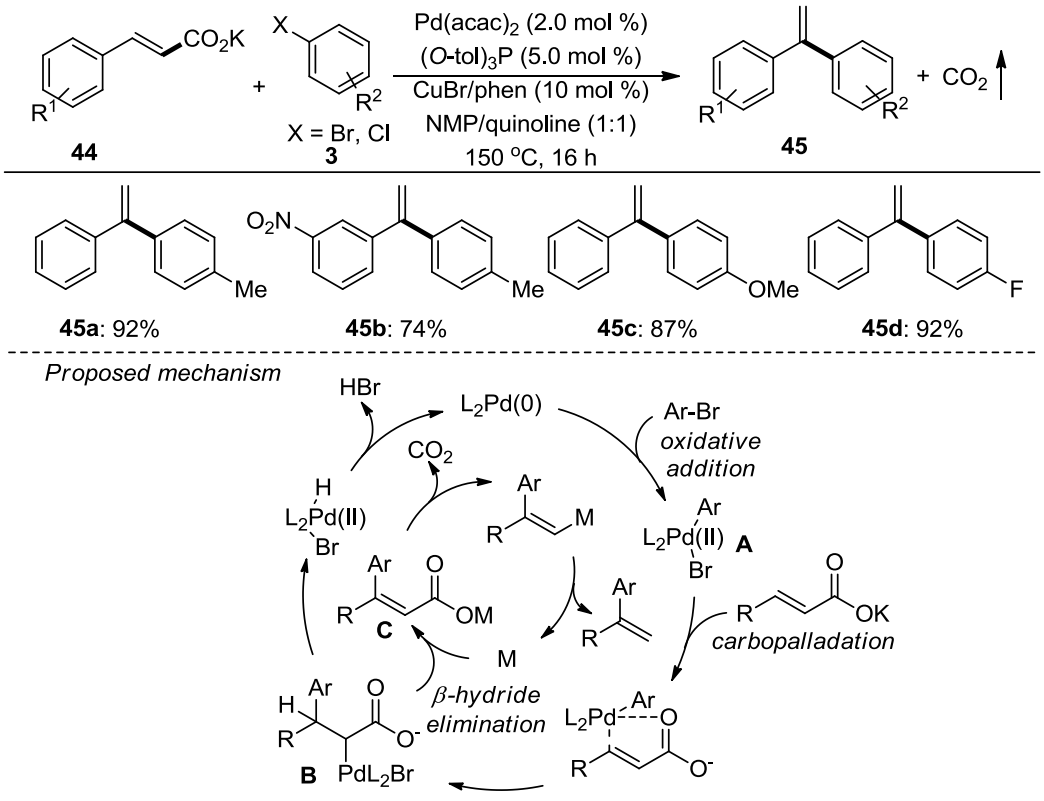
In 2009, Wu and coworkers first developed an efficient method for Pd-catalyzed decarboxylative arylation of cinnamic acids with aryl halides (Scheme 29).[72] The Pd/Ag bimetallic catalyst systems were used for this transformation. The mechanism of this alkenylation is similar to decarboxylative arylation using aromatic carboxylic acids. Presumably, silver mediates the extrusion of carbon dioxide affording alkenyl-silver species. Subsequently, transmetalation may occur with the aryl-Pd(II) intermediate which is formed via oxidative addition of Pd(0) to aryl halides resulting in the formation of alkenyl-aryl Pd(II) species which undergo reductive elimination to provide the desired product and regenerate the Pd(0) for next catalytic cycle.




**Scheme 29.** Pd/Ag-mediated decarboxylative arylation of cinnamic acids

Very recently, the Goossen's group has utilized the cinnamic acids and aryl halides for regioselective preparation of 1,1-diarylalkenes (Scheme 30).[73] Here, the carboxylate acts as a transient directing group to direct the arylation into a position opposite to that generally obtained by decarboxylative Heck reactions. For this

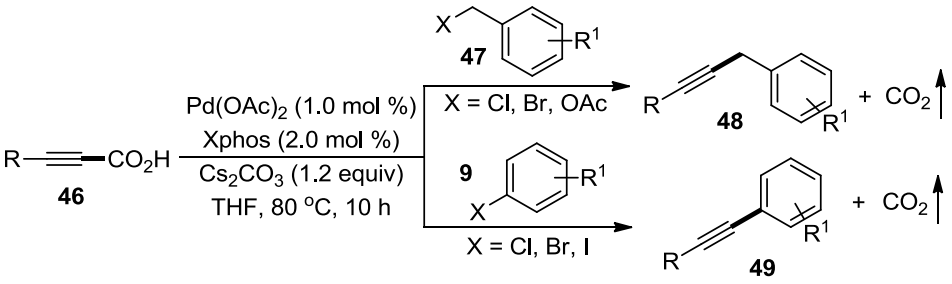
transformation, they have developed a bimetallic palladium(II)/Cu(I) catalytic system with sterically bulky and electron rich phosphorous ligand. To understand the reaction pathway they have done several control experiments and proposed the reaction mechanism as depicted in scheme 30. Initially, oxidative addition of Pd(0) to aryl halides affords aryl-Pd(II) species **A** which then reacts with cinnamic carboxylates generating the intermediate **B** via carbopalladation followed by alkene insertion and aryl migration. In this step carboxylate group directs the addition of aryl moiety at the *β*-position of the alkene. Then from the intermediate **B**, 1,1-disubstituted alkene carboxylates **C** is produces via *β*-hydride elimination. Finally, 1,1-disubstituted alkene carboxylate **C** undergoes decarboxylative protonation to yield the desired 1,1-diarylalkene. At the same time the Maiti group has also showed the same selectivity in the decarboxylative alkenylation reaction using unbiased simple arenes and cinnamic acids via C-H activation.[74]




**Scheme 30.** Decarboxylative 1,1-disubstituted alkenes synthesis

## I.8. Decarboxylative alkynylation reactions

Propiolic acids have been used in decarboxylative cross-coupling reactions for the introduction of alkyne moiety into the organic backbone.[75] This reaction is complementary to the typical Sonogashira cross-coupling reactions.[76] The decarboxylative cross-coupling reactions using alkynyl carboxylic acids go through under mild reaction conditions due its facile decarboxylative metalation process. Initially, the Li group has reported a palladium catalyzed decarboxylative cross-coupling between aryl halides/benzyl halides and propiolic acids for the synthesis of aryl alkynes (Scheme 31).[77] Because of the faster kinetics of the decarboxylation step, propiolic acids caught special attention for alkynylation reactions in the last decades. Details we discussed in **Chapter V**.

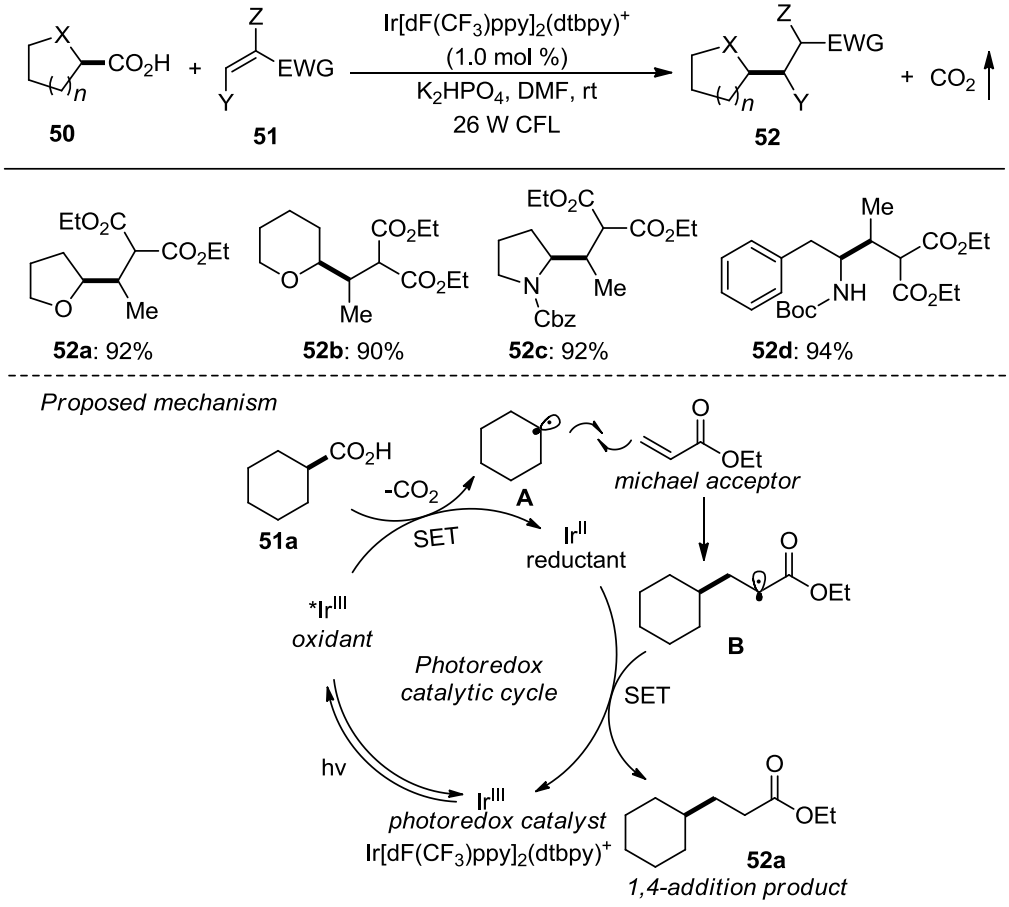



**Scheme 31.** Decarboxylative alkynylation reactions

## I.9. Decarboxylative cross-couplings using alkyl carboxylic acids

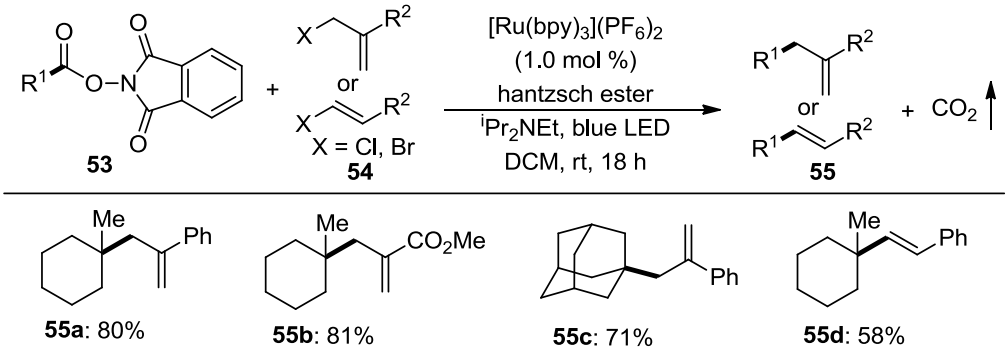
Very recently, not only aromatic carboxylic acids but also alkyl carboxylic acids have been used as a coupling partner in the decarboxylative cross-coupling reaction.[14,78] Decarboxylation of aliphatic carboxylic acids generally occurs through radical pathway under mild reaction conditions.[79] Taking full potential of this, a wide variety of photoredox catalytic systems as well as transition metal catalyst system have been developed for the decarboxylative cross-coupling using aliphatic carboxylic acids. In this vein, the MacMillan group has showed the generation of alkyl radical from alkyl carboxylic acid under photoredox conditions and subsequently they were able to use this alkyl radical with a variety of quencher to provide different types of C-C and C-heteroatom cross-coupled products.[80]

Very recently, a decarboxylative Michael-type 1,4-addition reaction between activated olefin and aliphatic carboxylic acids was reported by the same group in the presence of Ir-photocatalyst without requirement of others organometallic species (Scheme 32).[81] Initially, base-promoted deprotonation from the carboxylic acid to generate corresponding carboxylate and then subsequent oxidative single-electron transfer (SET) from the carboxylate to the photoactivated Ir-catalyst can generate a carboxyl radical. This carboxyl radical can easily produce nucleophilic alkyl radical **A** via decarboxylation process. Now, the alkyl radical can undergo conjugate 1,4-addition with an electron deficient Michael acceptor to form a new C-C bond through the generation of a new alkyl radical species **B**. Finally, reduction of **B** by Ir(III) species and subsequent protonation produces the desired 1,4-conjugate addition product with the regeneration of photocatalyst for next catalytic cycle (Scheme 32).

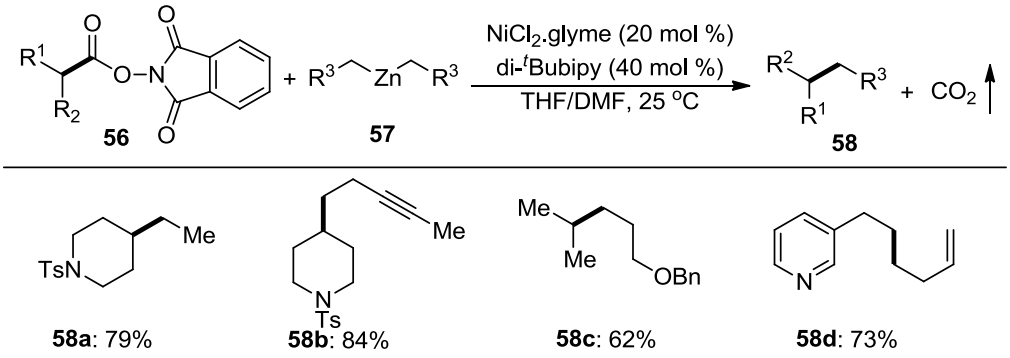



**Scheme 32.** Decarboxylative alkylation reaction using photoredox catalyst system

Allylation and vinylation reaction was also achieved successfully by the Overman group using allyl/vinyl halide and *N*-(acyloxy)-phthalimide derivatives of tertiary alkyl carboxylic acids in the presence of a Ru-photocatalyst and diisopropylethylamine (DIPEA) as a reductive quencher (Scheme 33).[82] A similar type of reaction has also been developed by the Chen group using allyl sulfone as surrogates of the allylating agent under photocatalytic condition.[83] Interestingly, primary, secondary, tertiary and also benzyl carboxylic acid derivatives were used as an efficient substrates in the reaction providing excellent yields.




**Scheme 33.** Decarboxylative allylation/vinylation of alkyl carboxylic acids




**Scheme 34.** Nickel-catalyzed decarboxylative alkyl-alkyl cross-coupling reaction

Recently, Baran group have developed an alkyl-alkyl decarboxylative cross coupling reaction between alkyl carboxylic acids and dialkylzinc reagents in the presence of nickel-catalyst (Scheme 34).[84] Dialkylzinc reagent is effective because of its facile transmetalation and ease of preparation from the corresponding alkyl halide. The redox-active esters can readily generate alkyl radical by accepting one electron via

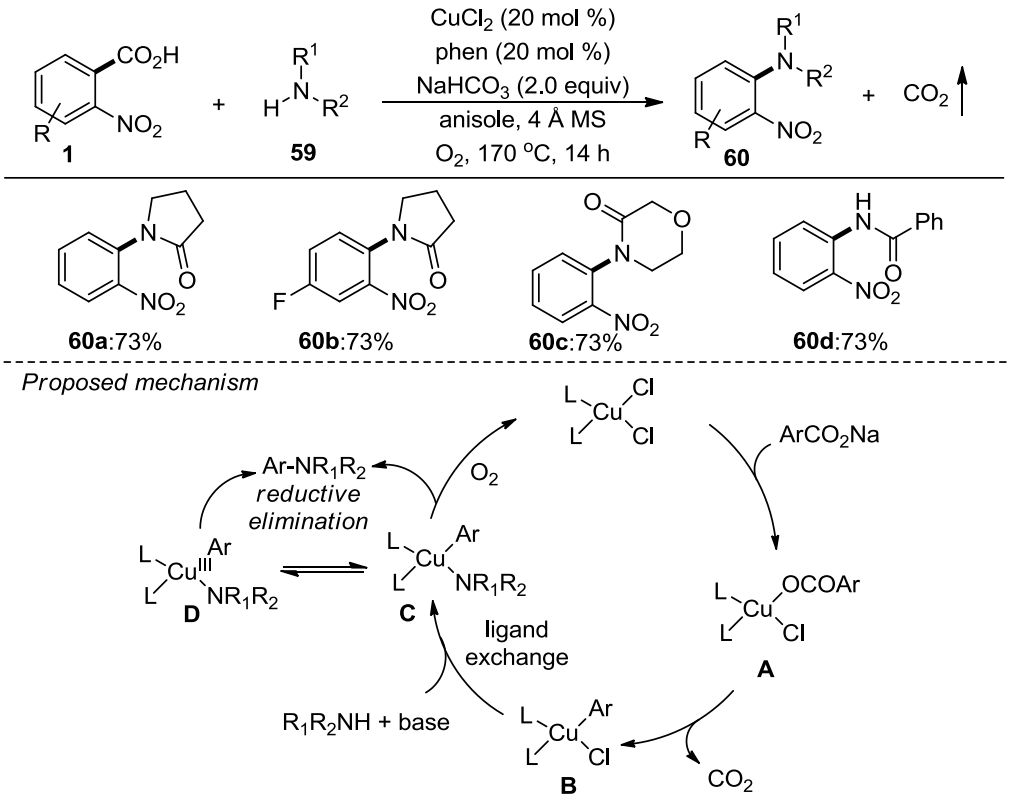
decarboxylation process in the presence nickel catalyst. Then this alkyl radical can couple with a low valent Ni-complex to produce the desired cross-coupled product via transmetallation with alkyl zinc reagents followed by reductive elimination.

## I.10. Decarboxylative C-heteroatom bond formation

Most of the decarboxylative couplings reactions have proceed through the formation of C-C bonds. There are also some examples of C-heteroatom bond forming decarboxylative cross-coupling reactions. These are discussed bellow-

## I.10a. Decarboxylative C-N bond formation

The preparation of aromatic amines have received much attention owing to their important role in the pharmaceutical, material, and dye industries.[85] In 2012, Zhang *et al*. have developed a novel method to prepare such aromatic amines via intermolecular decarboxylative process using aromatic carboxylic acids and *N*-nucleophiles (Scheme

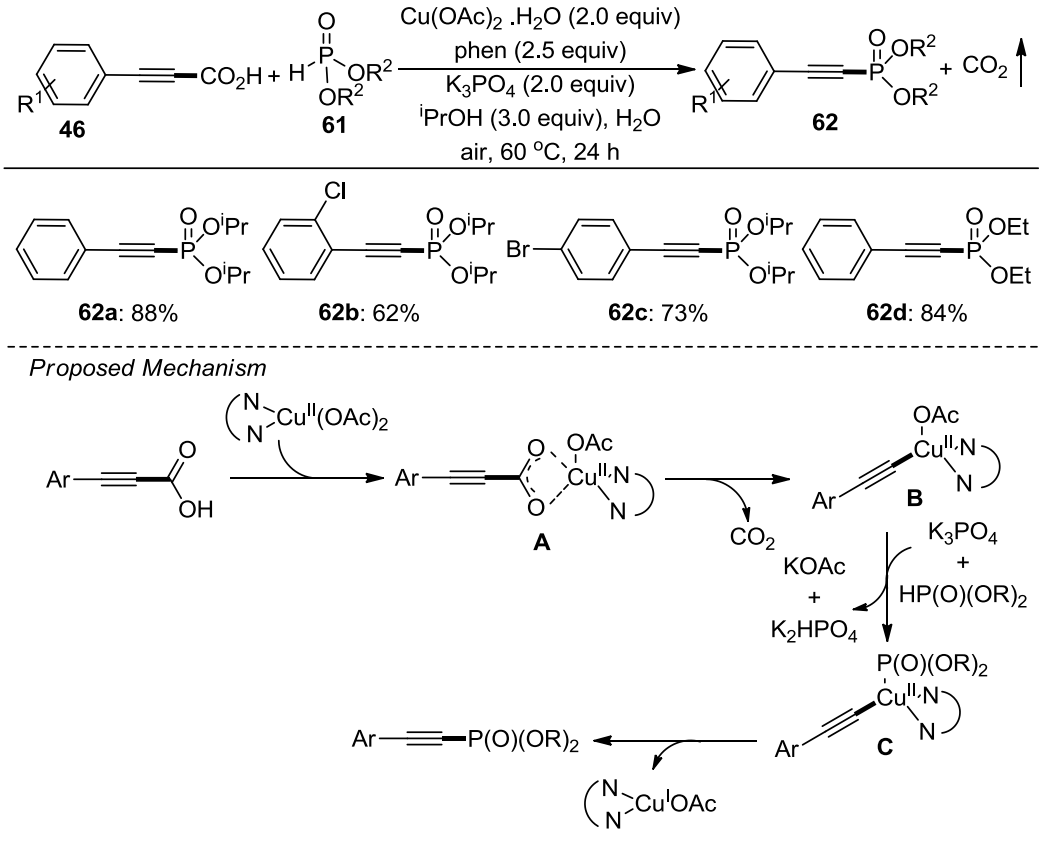



**Scheme 35.** Cu-catalyzed decarboxylative amination

35).[86] The reaction is catalyzed by copper(II)/phen combination in the presence of base and molecular oxygen ($O_2$). Here molecular oxygen acts as an oxidant for the catalytic turnover and copper is responsible for both decarboxylation as well as the C-N coupling. Mechanistically, they have found that the reaction proceed through decarboxylation/amination sequence which is shown in scheme 35. Very recently, another very interesting palladium-catalyzed intramolecular decarboxylative animation reaction has been reported by the Hu group.[87]

## I.10b. Decarboxylative C-P bond formation

The phosphorus-containing compounds are ubiquitously found in pharmaceuticals and bioactive products.[88] In 2014, the Wu group have developed a method for the synthesis of alkynylphosphonates via decarboxylation method using arylpropiolic acids and dialkyl *H*-phosphonates (Scheme 36).[89]

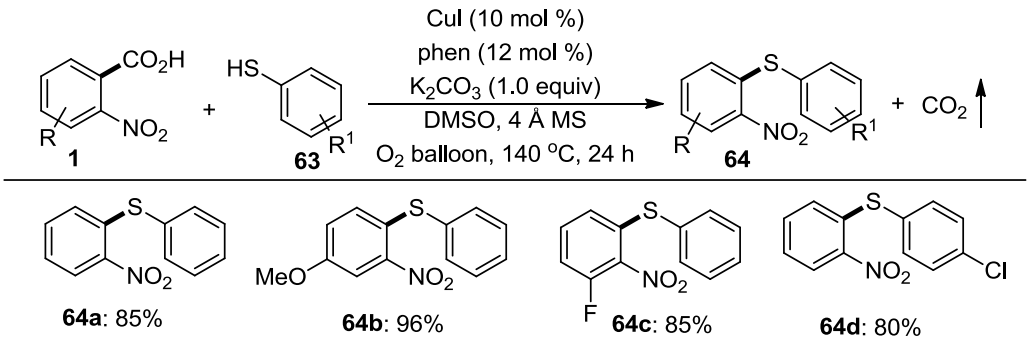



**Scheme 36.** Decarboxylative C-P bond formation

It has been observed that stoichiometric amount of $Cu(OAc)_2.H_2O$ and 1,10-phennanthroline ligand is essential to achieve synthetically useful yield. Interestingly, this decarboxylation reaction was occurred in water. To understand the reaction mechanism they have done several control experiments and proposed the reaction mechanism which is shown in scheme 36. First, the coordination of 1,10-phenanthroline to $Cu(OAc)_2$ generates active copper(II) intermediate and the ligand exchange occurs with the arylpropiolic acid to afford the copper(II) intermediate **A**, which is then undergo the copper mediated decarboxylation reaction to give copper(II) intermediate **B**. Then, the intermediate **B** reacts with a phosphonate anion which is generated from *H*-phosphonate and $K_3PO_4$ generating the copper(II) intermediate **C**. Finally, the reductive elimination of the intermediate **C** affords the desired product and the copper(I) species.

## I.10c. Decarboxylative C-S bond formation

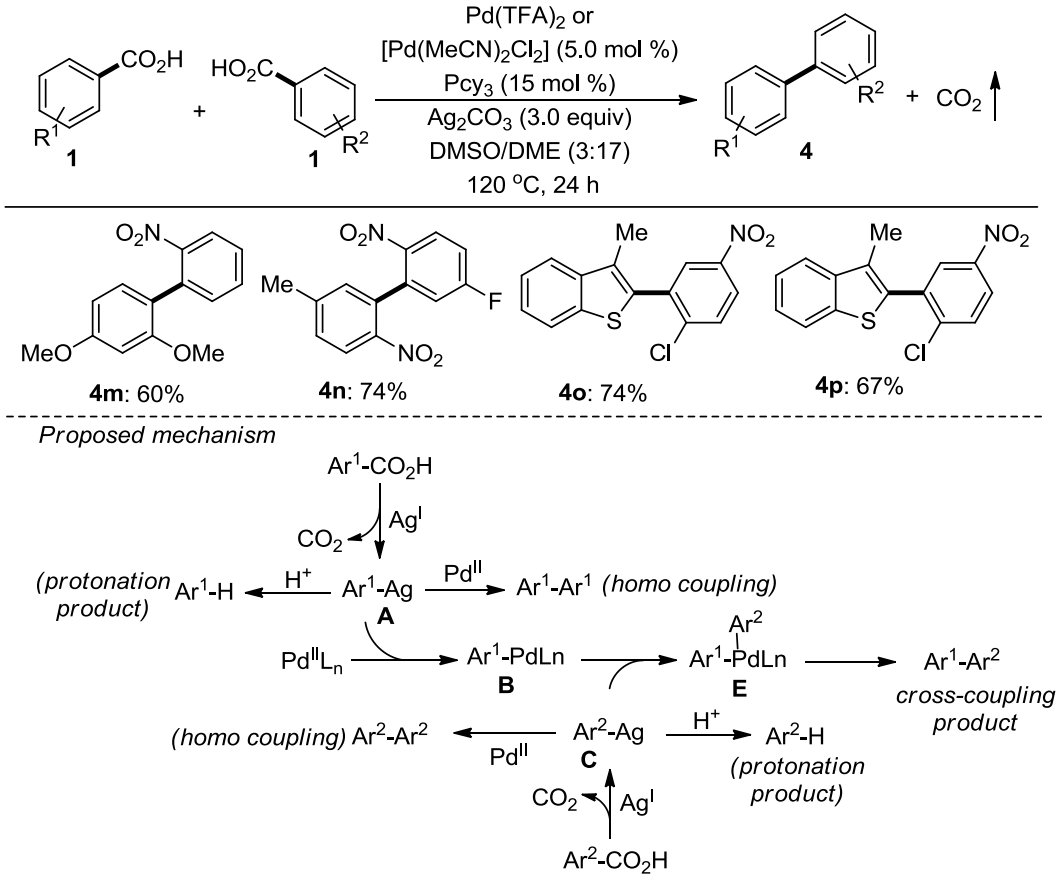
The aryl sulfides moiety also have broad applications in pharmaceutical and materials science.[90b] In addition, this compounds are used as intermediates in organic synthesis.[90a] Recently, the Hoover group have successfully achieved copper-catalyzed decarboxylative thiolation of aromatic carboxylic acids with thiols under molecular oxygen (Scheme 37).[91] Here molecular oxygen used as a sole oxidant for this transformation. From the control experiments it was found that diaryldisulfide was formed in situ during the course of the reaction.




**Scheme 37.** Cu-catalyzed decarboxylative thiolation

## I.11. Double decarboxylative cross-coupling reaction

The decarboxylative cross-couplings between carboxylic acid derivatives and simple arenes are attractive because of their ready availability and inexpensiveness. However, because of the abundance of multiple C-H bonds in the arenes moiety, regioselectivity problems arise as a negative outcome. To circumvent the regioselectivity issue, a second carboxylic acid can be used as coupling partner and the reaction may proceed via double decarboxylation.




**Scheme 38.** Pd(II)-catalyzed double decarboxylative cross-coupling reaction

The Su group have successfully developed an efficient method for the double decarboxylative cross-coupling process using electronically variant two aromatic carboxylic acids (Scheme 38).[92] The reaction is catalyzed by Pd(II) in the presence of bulky phosphorous ligand in DME/DMSO solvent. Here stoichiometric amount of $Ag_2CO_3$ is used not only as oxidant for catalytic turnover but also used for

decarboxylation. They have found excellent reactivity towards cross-coupling products rather than homocoupling products.

## I.12. Conclusion

The development of transition metal-catalyzed decarboxylative cross-coupling reactions for the formation of C-C and C-heteroatom bonds has made significant progress over the last decade. Most of the decarboxylative cross-coupling reactions proceed through the formation of well-defined carbon-metal bonds via catalytic process and offers several advantages including the avoidance of using air sensitive or expensive organometallic reagents compare to typical cross-coupling reactions. Despite remarkable progresses on this field, the major drawback of this protocol is that most of the decarboxylative cross-coupling reactions require high reaction temperature and harsh reaction conditions which restricts their application in the synthesis of complex molecular frameworks. To further expand the scope of decarboxylative cross-coupling reactions in organic synthesis as a standard tool, several challenges must be overcome. First the reaction temperature needs to be lowered and the catalyst loading needs to be reduced. Secondly, the substrate scope of the reactions should be generalized with using new catalytic systems. Further efforts need to be focused toward the investigation of decarboxylative cross-coupling reactions involving aliphatic carboxylic acids. Thirdly, another important development will be to extend the decarboxylative cross-coupling reactions using less expensive transition metals like Co, Fe and Ni.

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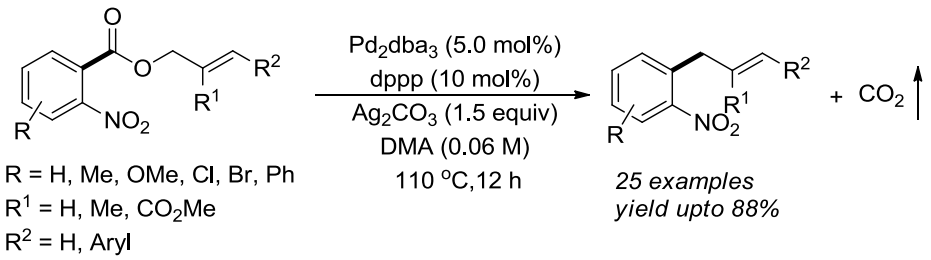
# CHAPTER II

## Palladium(0)-Catalyzed Intramolecular Decarboxylative Allylation of Ortho Nitrobenzoic Esters




***Abstract***: A Pd/Ag bimetallic system has been developed for the decarboxylative allylation of *ortho*-nitrobenzoic esters in intramolecular fashion. In contrast to the typical $sp^2$-$sp^3$ cross-coupling approach which requires air and moisture sensitive preformed organometallic reagents, we provide an alternative route to the synthesis of *ortho*-allyl nitroarenes from the corresponding *ortho*-nitrobenzoic acid derivatives. The reaction proceeds through a mechanistically distinct decarboxylative metalation pathway. A cooperative reactivity of palladium and silver is crucial for the reaction outcome.

1. Hossian, A.; Singha, S.; Jana, R. *Org. Lett*. **2014**, *16*, 3934-3937.

# Palladium(0)-Catalyzed Intramolecular Decarboxylative Allylation of Ortho Nitrobenzoic Esters

## II. 1. Introduction

Allylic aromatic compounds are ubiquitous structural motifs found in various natural products (Figure 1).[1] In addition, these compounds represent important organic intermediates to the synthesis of complex molecular frameworks due to the versatility of olefin functionalizations.[2] In the past decades, several methods have been used to construct the allylic arenes (Scheme 1). In particular, the transition metal catalyzed allylation of aryl metal species with allylic electrophiles provided the allylated arenes.[3] Although this protocol is valuable but suffer from the preactivation of arenes which needs stoichiometric amount of metal. Alternatively, the Lewis acid-catalyzed Friedel-Crafts aromatic allylation reaction is useful because it avoids the prior preparation of the aryl metal species from the arenes.[4] But, these protocols are limited to substrate scope and harsh reaction conditions. The mild Tsuji-Trost allylation reaction has also attracted attention towards the synthesis of allylated arenes.[5] Recently, taking the advantages of C-H activation method, the transition metal catalyzed allylation reactions via C-H activation have been developed using various allylic surrogates.[6] However, the C-H bond activation methods require installation of directing groups in the substrates to control regioselectivity and their subsequent removal prohibits the synthetic fidelity. To overcome this problem, a regioselective, decarboxylative allylation reactions using inexpensive, commercially available, air and moisture stable aromatic carboxylic acids has been developed.

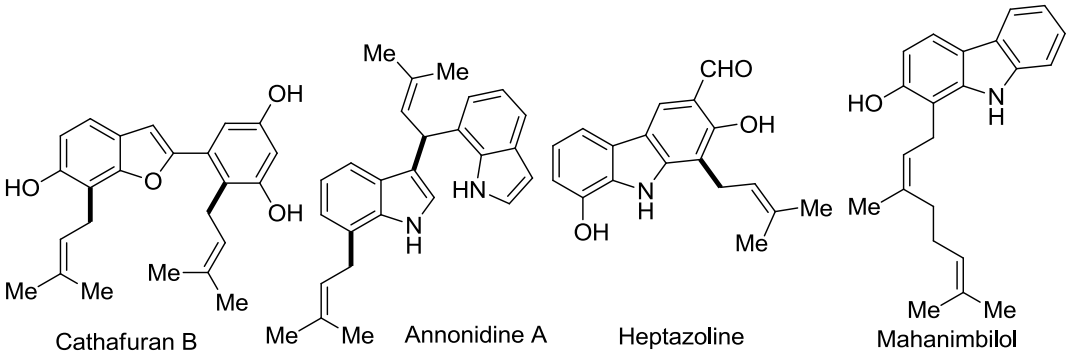
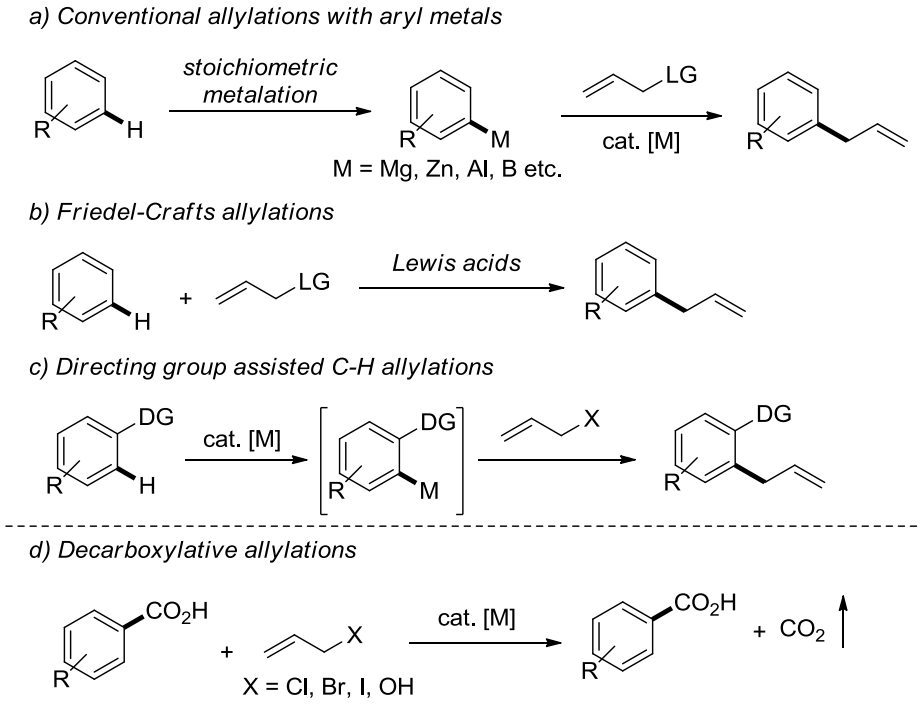


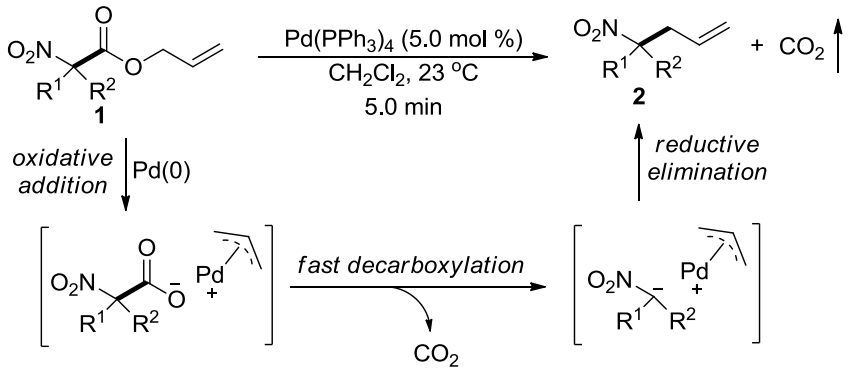
**Figure 1.** Some selected examples of naturally occurring allylated products




**Scheme 1.** Synthesis of aromatic allylic compounds

## II. 2. Review

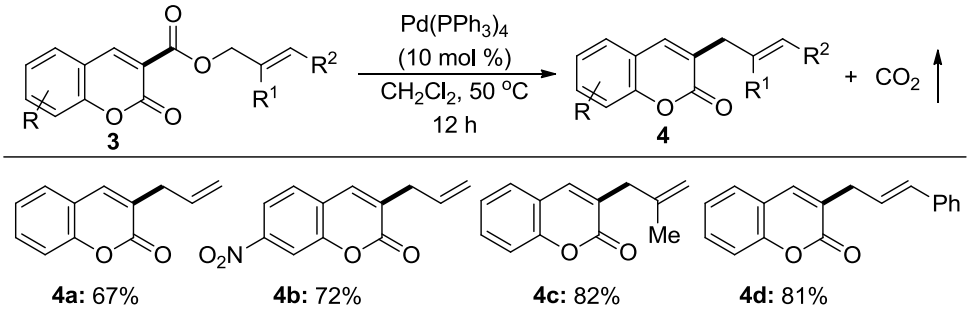
The palladium-catalyzed decarboxylative $sp^3$-$sp^3$ allylic alkylation has been widely explored.[7] In $sp^3$-$sp^3$ allylation reaction, the incipient anion generates after decarboxylation, which is stabilized by the proximal electron withdrawing groups. In this vein the Tunge group have showed that the allyl nitroacetic esters in the presence of 5.0




**Scheme 2.** Decarboxylative allylation of allyl nitroacetic esters

mol % $Pd(PPh_3)_4$ undergoes decarboxylative allylation to provide the desired allylation products with excellent yield (Scheme 2).[8] A wide range of *α,α*-dialkyl substrates as well as an *α*-phenyl *α*-fluoro ester participate in the reaction smoothly. Here the incipient anion after decarboxylation is stabilized by the proximal nitro group in the reaction. However, the other functional groups such as keto,[9] ester,[10] cyano,[11] sulfone,[12] etc. have been utilized for such stabilization in $sp^3$-$sp^3$ decarboxylative allylation reactions.

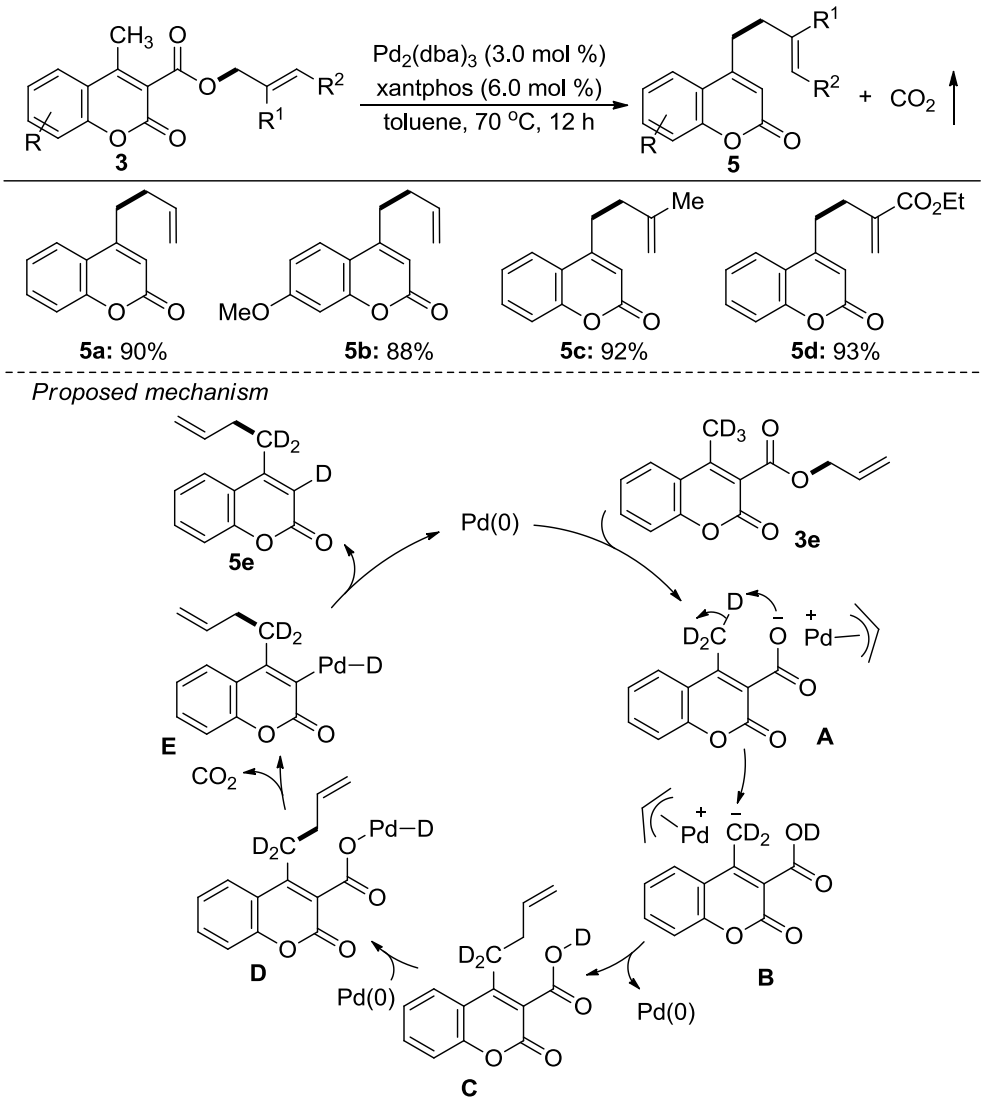
The decarboxylative $sp^2$-$sp^3$ allylation using arene carboxylic acids is not reported earlier due to the instability and rapid protonation of the anion on the $sp^2$-carbon which is generated after decarboxylation. Therefore, selective $sp^2$-$sp^3$ decarboxylative allylation is an extremely challenging target to achieve. In this vein, Jana *et al.* reported a palladium catalyzed decarboxylative allylation of allyl esters of 3-carboxylcoumarins moiety to furnish allylation product under very mild reaction condition (Scheme 3).[13] The reaction is very interesting due to the formation of functionalized coumarins which are privileged structures in biomedical sciences.[14] Here the anion on $sp^2$-carbon which is formed after decarboxylation is stabilized by the proximal keto ester group present in the coumarin moiety and regioselective allylation occurred selectively at the C3-carbon of coumarins.




**Scheme 3.** Decarboxylative allylation of allylic ester of coumarins

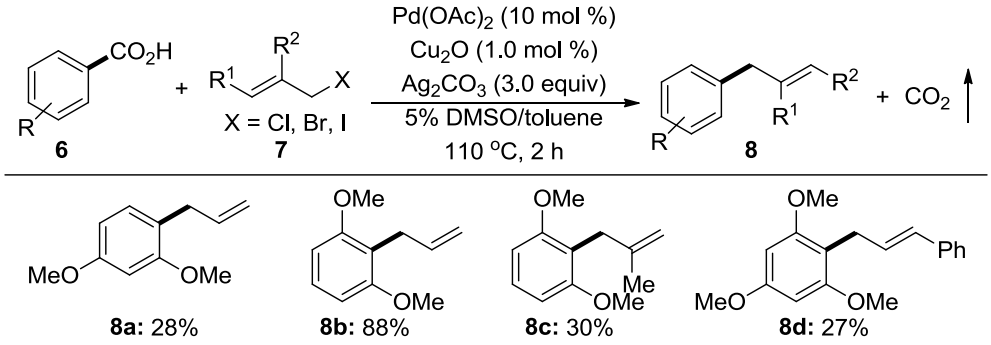
Interestingly, when 4-methyl-3-allylcoumarate was used, the reaction did not furnish any desired C3-allylation product instead a migratory $sp^3$-$sp^3$ cross-coupling product was formed. Presumably, this is due to the destabilization of the C$sp^2$ anion which prefers to migrate at the $sp^3$-carbon through proton exchange. After rigorous screening, they optimized reaction conditions for this remote decarboxylative *γ*-allylation of the coumarins moiety in good to excellent yields of allylation product with excellent

selectivity at $sp^3$ center (Scheme 4).[15] To understand the mechanism for this unusual decarboxylative $\gamma$-allylation they performed several control experiments Scheme 4. First palladium undergoes oxidative addition with substrates to form a $\pi$-allyl palladium complex and the coumarin carboxylate **A**. Then intramolecular 1,5-proton transfer occurs to generate a stabilized carbanion at the C4-carbon **B**. Next, nucleophilic substitution or reductive elimination of the $\pi$-allyl palladium complex forms the C-C bond at C4 position. Finally, palladium catalyzed decarboxylative protonation occurs at C3 position.

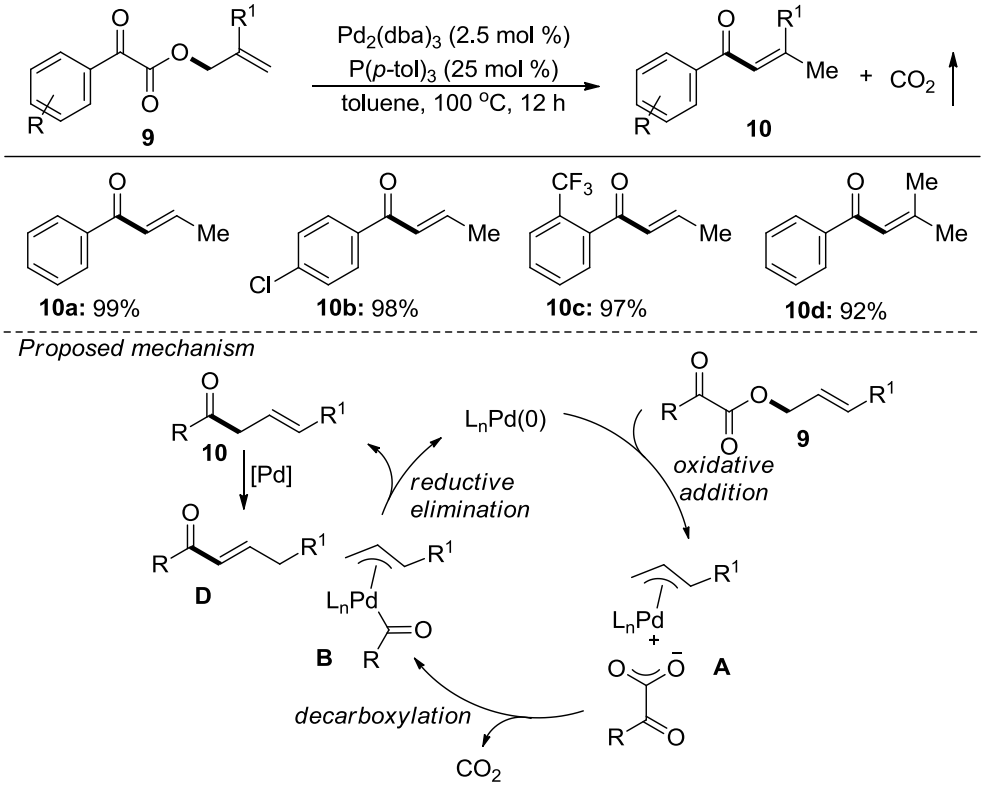



**Scheme 4.** Migratory decarboxylative $\gamma$-allylation of coumarins

The liu group also reported a palladium catalyzed intermolecular $sp^2$-$sp^3$ decarboxylative allylation using arene carboxylic acids and allyl bromides (Scheme 5).[16] However, the methodology was limited to electron-rich substrates mainly and moderate to low yield of the desired product was obtained. Mechanistically, aryl-palladium species is generated through palladium mediated decarboxylation and subsequently nucleophile attacks to an allyl halide to give the desired aromatic allylated product.



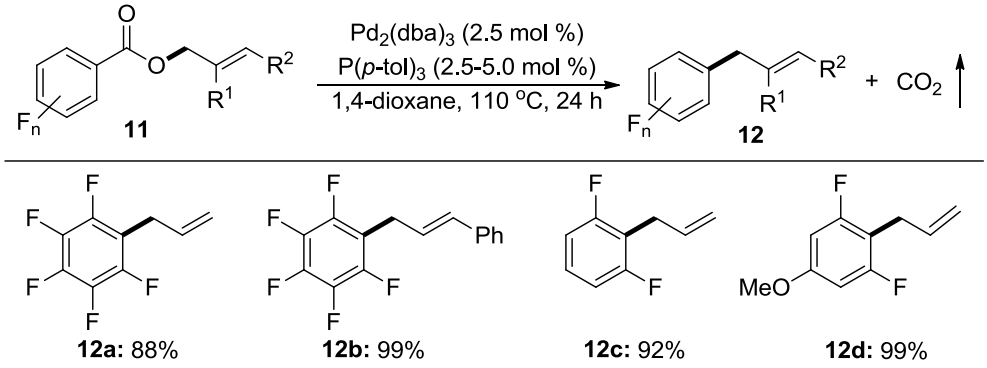

**Scheme 5.** Palladium-catalyzed intermolecular decarboxylative allylation




**Scheme 6.** Palladium-catalyzed decarboxylative allylation of α-oxocarboxylates

In 2011, Goossen and coworkers have developed a palladium catalyzed decarboxylative $sp^2$-$sp^3$ allylation of non-activated $\alpha$-oxocarboxylates resulted in $\alpha,\beta$-unsaturated ketones through alkene isomerization (Scheme 6).[17] Interestingly, here $\alpha$-oxocarboxylic acid serve as a acyl anion donor for this transformation. Initially, oxidative addition of the carboxylates substrate to Pd(0) lead to the formation of $\pi$-allyl-Pd-carboxylate complexes **A**. From the complex **A,** an extrusion of $CO_2$ leads to the formation of the acyl $\pi$-allyl-Pd complex **B**. Finally, reductive elimination of the acyl $\pi$-allyl-Pd complex affords the allyl ketone **10**, which is then isomerize to the corresponding conjugated vinyl ketone **D** in the presence of palladium (Scheme 6).

Recently, the Goossen's group has showed a decarboxylative $sp^2$-$sp^3$ allylation of arene benzoates under palladium catalysis (Scheme 7).[18] For this transformation no stoichiometric additive is required and the reaction proceeds under mild conditions. In the reaction only fluorinated benzoates provided good to high yield of the desired allylation product with excellent linear selectivity. However, other electron deficient benzoates like allyl ester of nitrobenzoic acids did not provide any desired product.

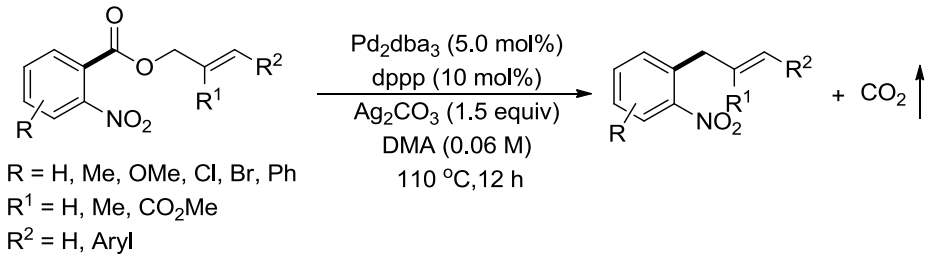



**Scheme 7.** Palladium-catalyzed decarboxylative allylation of fluorinated benzoates

## II. 3. Present work

Aromatic nitro compounds are useful intermediates for the synthesis of agrochemicals, pharmaceuticals, dyes, photo-reactive compounds, high energetic materials, radiopharmaceutical tracers, etc.[19] A facile reduction of the aromatic nitro groups to their corresponding anilines provides common starting materials for the syntheses of a plethora of *N*-heterocycles and natural products.[20] Despite their interesting properties, access to

*ortho*-substituted nitroarenes is limited due to inherent incompatibility with some organometallic reagents.[21] To overcome this problem the Knochel group introduced an elegant approach for the generation of nitro-containing organometallics via I-Mg exchange.[22] However, this protocol suffers from serious limitations such as the use of air and moisture sensitive preformed organometallic reagents, highly toxic copper(I)cyanide and expensive organohalides. Therefore, alternative routes to the synthesis of *ortho*-allylnitroarenes using inexpensive, air and moisture stable starting materials are in high demand. Recently, nitrobenzoic acid derivatives have been widely used in palladium-catalyzed decarboxylative cross-coupling reactions.[23] Therefore, synthesis of *ortho*-allylnitroarenes using *ortho* nitrobenzoic acids through novel decarboxylative allylation reaction will be attractive in view of practical applicability. We hypothesized that the nitro group at the *ortho* position could be beneficial in decarboxylative allylation as it can stabilize the aryl anion which is formed after decarboxylation.



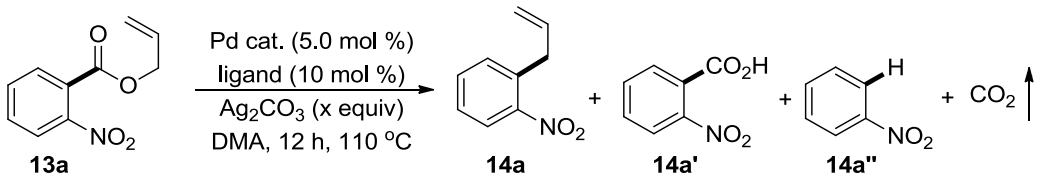

**Scheme 8.** Palladium-catalyzed intramolecular decarboxylative allylation of *ortho* nitrobenzoic esters

## II. 4. Results and discussion

We started optimization of the reaction conditions by heating a mixture of ortho-nitrobenzoic acid and allyl bromide and a catalytic amount of Pd(0) at 160 $^{o}$C, but no allylation product was formed. Switching to allyl acetate from allyl bromide resulted in a trace amount of allylation product along with nitrobenzene as a major product. We realized that the carboxylic acid proton could be detrimental for the allylation product formation and may lead to the undesired decarboxylative protonation product. Therefore, the potassium salt of the corresponding nitrobenzoic acid was employed but unfortunately, no allylation product was observed. Next, allyl ester of the corresponding

acid was prepared and subjected to the intramolecular decarboxylative allylation (Table 1). Interestingly, all starting material was consumed and a mixture of corresponding allyl and styrenyl products was isolated in slightly improved yield (entry 18, Table 1). Still, the undesired *ortho*-nitrobenzoic acid and nitrobenzene were formed predominantly. The poor mass balance toward allylation product can be attributed due to decomposition of the $\pi$-allyl-Pd species[24] and double bond isomerization at elevated temperature to generate undesired styrenyl product. Therefore, we decided to use the silver(I) salt as an additive since it is known to promote decarboxylation at lower temperature[25] and decreases double bond isomerization.[26] Gratifyingly, yield was improved to 55% with the addition of only 10 mol % of the silver carbonate (entry 5, Table 1). After a rigorous study with catalyst, ligand, solvent and the amount of additive the allylation product was isolated in excellent yields using a combination of 5 mol % $Pd_2dba_3$, 10 mol % dppp with 1.5 equiv of $Ag_2CO_3$ in DMA at 110 $^oC$.

**Table 1.** Optimization of the reaction conditions[a]

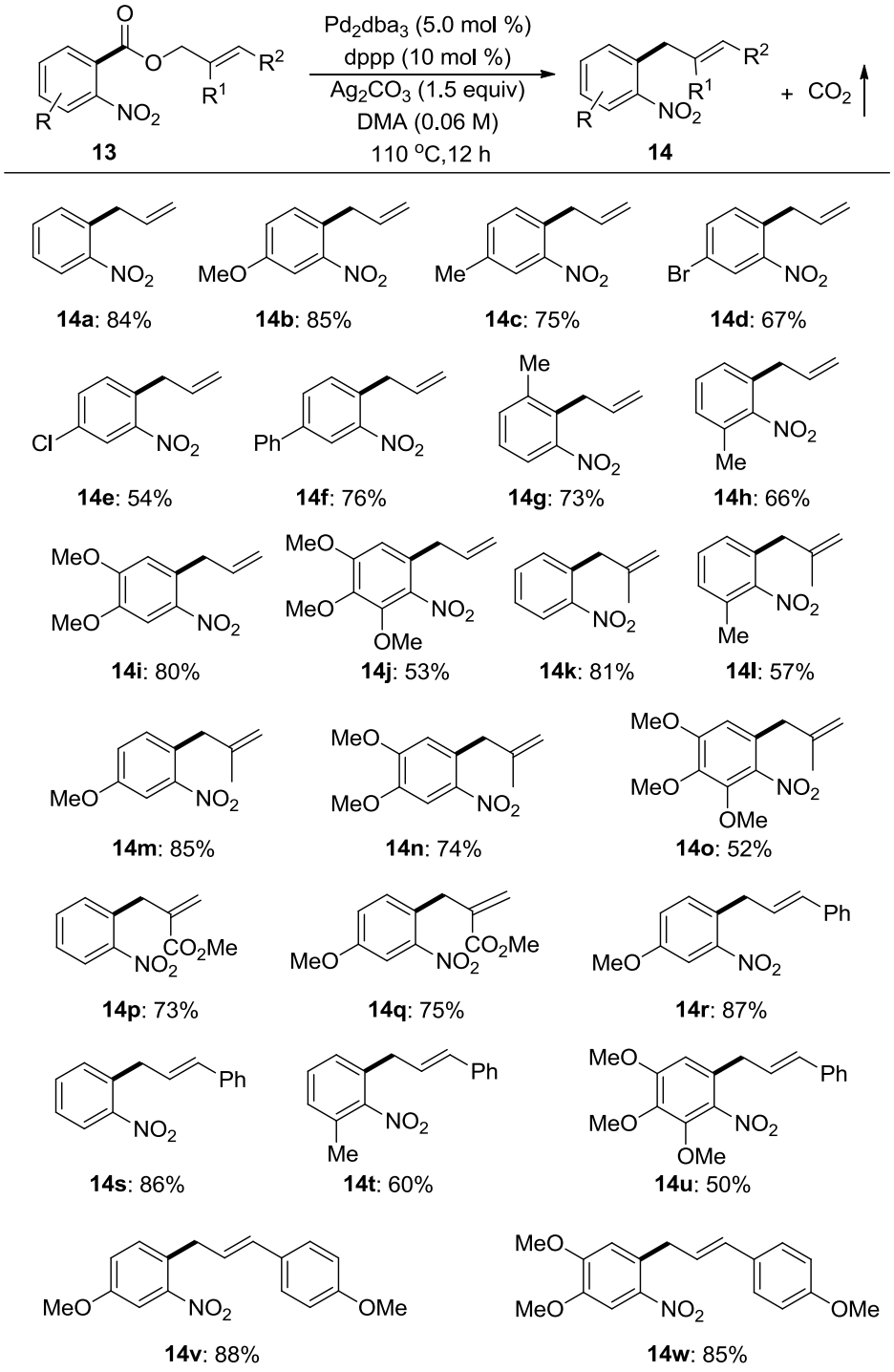



| entry | Pd cat. | ligand | x | yield (%)[b] | **2a**:**2a'**:**2a"**[b] |
|---|---|---|---|---|---|
| 1[c] | $Pd(PPh_3)_4$ | - | 0 | 0 | - |
| 2[c] | $Pd(PPh_3)_4$ | - | 0.2 | 30 | 70:10:20 |
| 3[c] | $Pd(OAc)_2$ | - | 0.2 | 0 | - |
| 4[c] | $Pd(tfa)_2$ | - | 1.5 | 0 | - |
| 5 | $Pd_2dba_3$ | xantphos | 0.1 | 55 | 80:7:13 |
| 6 | $Pd_2dba_3$ | dppf | 0.1 | 50 | 75:10:15 |
| 7 | $Pd_2dba_3$ | *rac*-BINAP | 0.1 | 63 | 73:7:20 |

| | | | | | |
|---|---|---|---|---|---|
| 8 | $Pd_2dba_3$ | dppp | 0.1 | 68 | 82:10:8 |
| 9 | $Pd_2dba_3$ | dppp | 0.5 | 72 | 85:6:9 |
| 10 | $Pd_2dba_3$ | dppp | 1.0 | 80 | 85:5:10 |
| 11 | $Pd_2dba_3$ | dppp | 1.5 | 90 | 94:0:6 |
| 12 | $Pd_2dba_3$ | dppp | 2.0 | 88 | 92:0:8 |
| 13 | $Pd_2dba_3$ | dppe | 1.5 | 40 | 78:13:9 |
| 14 | $Pd_2dba_3$ | dppb | 1.5 | 50 | 80:12:8 |
| 15 | $Pd_2dba_3$ | $PCy_3$ | 1.5 | 45 | 82:10:8 |
| 16 | $Pd_2dba_3$ | xphos | 1.5 | 60 | 77:13:10 |
| 17[d] | $Pd_2dba_3$ | dppp | 0 | 0 | - |
| 18[e] | $Pd_2dba_3$ | dppp | 0 | 55 | 30:43:27 |
| 19 | $Pd(tfa)_2$ | dppp | 1.5 | 48 | 63:27:10 |
| 20[f] | $Pd(tfa)_2$ | - | 3.0 | 7 | - |

[a]All reactions were carried out in 0.1 mmol scale, in DMA 0.06 M. [b]Yields refer to here are overall isolated yields and product distributions were determined by $^1$H NMR of the crude product. [c]10 mol % of the Pd catalyst was used. [d]100 mol % of the $Pd_2dba_3$ and 200 mol % of the dppp was used. [e]The reaction was heated at 160 $^oC$, mixture of allyl and styrenyl product was isolated. [f]20 mol % of $Pd(tfa)_2$, DMF:DMSO (19:1), 120 $^oC$.

Under the optimized reaction conditions, we explored substrate scope for the decarboxylative allylation reaction (Scheme 9). A variety of substituted nitroarenes allow the formation of allylation products in good to excellent yields. A careful study revealed that electron donating substituents such as *p*-OMe on *o*-nitrobenzoate favours allylation product formation (**14b**, **14m**, **14q**, **14r**, **14v**, Scheme 9) and two *m*-OMe groups which are electron withdrawing in nature, lower the yields to some extent (**14i**, **14n**, **14w**,

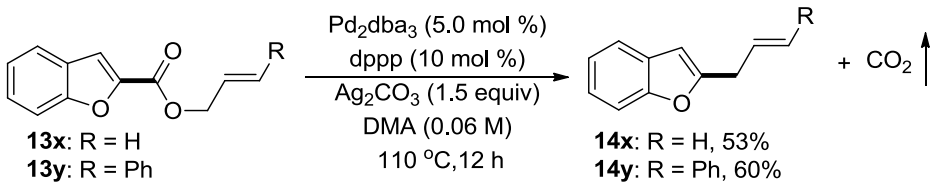



**Scheme 9.** Substrate scope of decarboxylative allylation.

*Note*: All reactions were carried out in 0.3 mmol scale. Yields refer to the average of isolated yields of at least two experiments.

Scheme 9). However, yields of the allylation products are decreased drastically with a substitution of three adjacent -OMe groups due to low conversion, substantial amounts of protonation product and carboxylic acid formation (**14j**, **14o**, **14u**, Scheme 9). Substrates with electron-deficient substituent, e.g. 2,4-dinitro benzoic ester resulted in decarboxylative protonation product only. Therefore, electron-withdrawing substituents on the *o*-nitro-benzoate facilitate decarboxylation but they decrease the ability of the aryl anion to serve as a $\sigma$-donor for the Pd(II)allyl cation. Halogen substituents, such as Br, Cl are compatible with the reaction conditions (**14d**, **14e**, Scheme 9) which may undergo further cross-coupling reactions. In addition to the cross-couplings of unsubstituted allyl esters, a variety of substituted and functionalized allyl esters also underwent couplings to provide allylation products (**14k**-**14q**, Scheme 9). Allyl esters from the corresponding cinnamyl alcohols and its derivatives produced the linear product selectively (**14r**-**14w**, Scheme 9). However, allyl esters that possess $\beta$-hydrogens such as crotyl, prenyl, 2-cyclohexenyl esters preferentially formed conjugated dienes via $\beta$-hydrogen elimination and protonation product[6g]. A selective reduction of the nitro group afforded *o*-allyl aniline in excellent yields (procedure in experimental section).

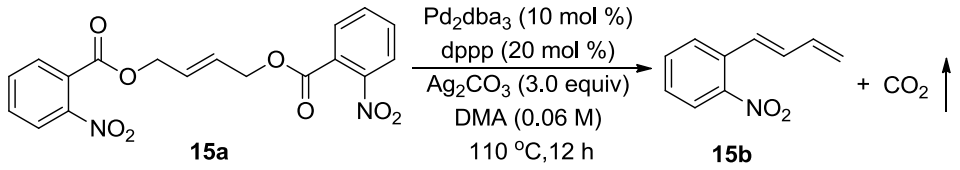
Subsequently, several heteroaromatic carboxylic esters were tested under the reaction conditions. Unfortunately, nitrogen-containing heterocycles such as indole and pyridine-2-carboxylic esters did not furnish any desired product. However, benzofuran-2-carboxylic esters furnished allylation product in good to moderate yields (Scheme 10).




**Scheme 10.** Decarboxylative allylation of benzofuran-2-carboxylates

The decarboxylative allylation reaction with crotyl, prenyl, 2-cyclohexenyl esters afforded protonation product formation exclusively and consistently. After, $\beta$-hydrogen elimination the allyl part forms gaseous or highly volatile 1,3-diene compounds which is difficult to isolate. Therefore, we performed the reaction with **15a**, Scheme 11 which

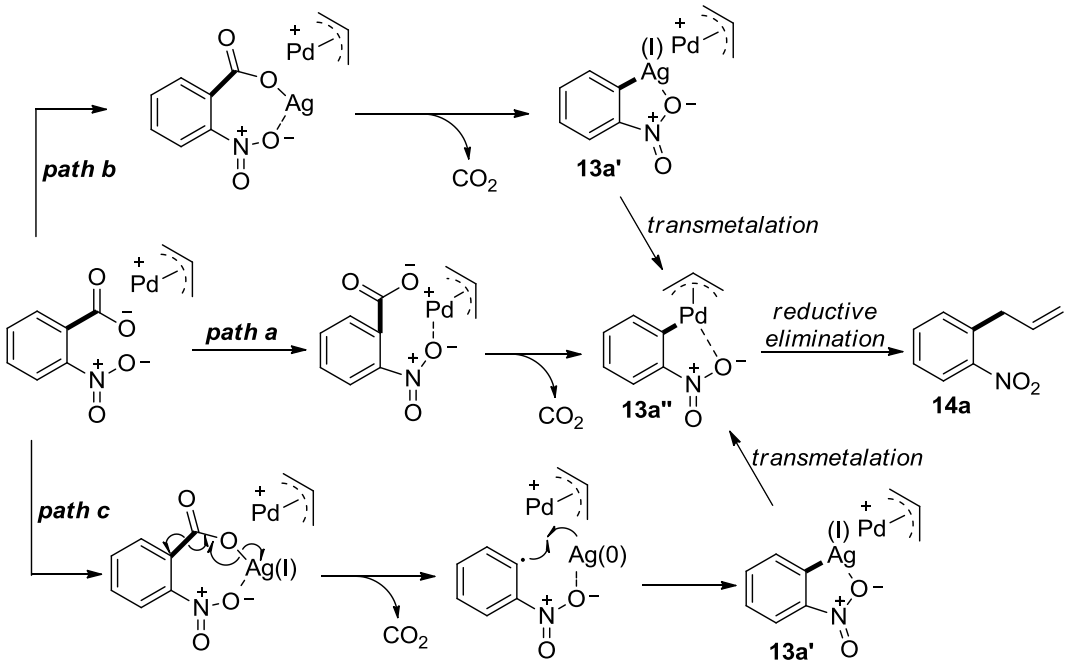
contains a *β*-hydrogen and the corresponding diene **15b** was isolated to confirm *β*-hydrogen elimination.




**Scheme 11.** Decarboxylative allylation and β-hydride elimination to 1,3-diene formation

## II. 5. Investigation of the reaction mechanism

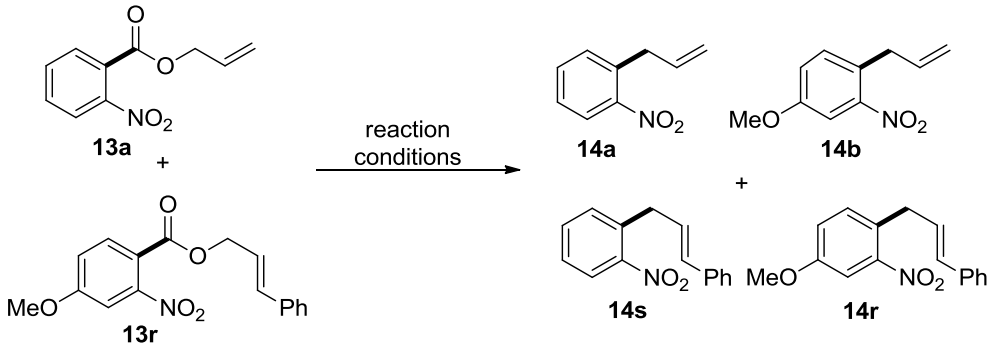
Next, we turned our attention to gaining insight of the reaction mechanism. After oxidative addition of palladium(0) to the allyl ester **13a** the reaction may proceed in three distinct pathways. In ***path a***, the solvent-separated ion pair may undergo decarboxylation via a two-electron process[27] followed by carbopalladation to generate **13a"** which is converted to the desired product after reductive elimination. Whereas, in ***path b***, a silver-assisted decarboxylation via anionic route can generate the aryl-silver species **13a'** which can undergo transmetalation with palladium followed by reductive elimination to furnish




**Scheme 12.** Possible mechanistic pathways

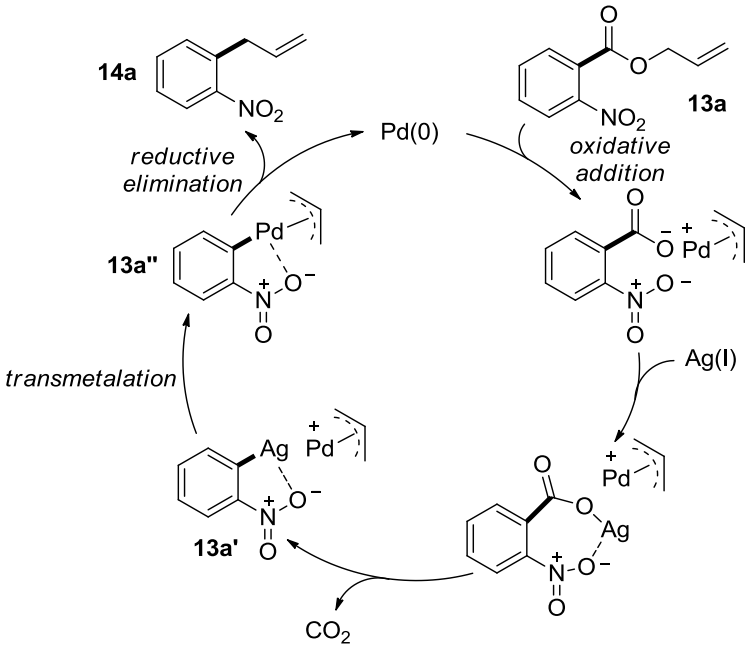
allylation product. Alternatively, this silver-assisted decarboxylation may proceed via Hunsdiecker-type free radical pathway as depicted in ***path c*** (Scheme 12). The *ortho*-nitro group can stabilize to either the organosilver(I) or organopalladium(II) prior to and after decarboxylation through coordination.

To elucidate, several control experiments were performed. Heating the reaction mixture at 110 $^{o}$C without any silver salt resulted in only nitrobenzoic acid. Even a stoichiometric amount of palladium also failed to promote decarboxylation at this temperature (entry 17, Table 1). Whereas, heating the reaction mixture at 160 $^{o}$C with catalytic amount of palladium afforded the desired product albeit in low yield (entry 18, Table 1). On the other hand, when *ortho*-nitro benzoic acid was heated at 110 $^{o}$C only with the silver carbonate the nitrobenzene was formed indicating silver-assisted decarboxylation. To elucidate further, the reaction was carried out under the standard reaction conditions in the presence of 1.0 equiv of TEMPO, a radical scavenger. Almost the same yield of **14a** as under the standard conditions (84%) was obtained, which rules out the radical mechanism as shown in ***path c***. When Pd(II)/Ag(I) was used in lieu of Pd(0)/Ag(I), only starting material was recovered which indicates that Pd(0) is essential to initiate the reaction (entry 20, Table 1). An extensive cross-over was also observed between two structurally disparate allyl esters. It supports that the solvent-separated ion pairs are formed and undergo all possible combinations to provide the cross-over products (Scheme 13).




**Scheme 13.** Cross-over experiment

Based on these observations, we presumed that the reaction may proceed through ***path a*** at an elevated temperature whereas in ***path b*** under Pd/Ag bimetallic system at a lower temperature. Initially, palladium(0) undergoes an oxidative addition to the allyl ester 1a to form a $\pi$-allyl-Pd complex and *ortho*-nitrobenzoate anion. Subsequently, silver salt of the corresponding *ortho*-nitrobenzoic acid may form and undergo Ag(I)-assisted decarboxylation to afford the corresponding aryl-Ag species **13a'**. A transmetalation between aryl-Ag and $\pi$-allyl-Pd complex generates an aryl-Pd species **13a''**. Finally, reductive elimination yields the desired allylation product and the Pd(0) to complete the catalytic cycle (Scheme 14).

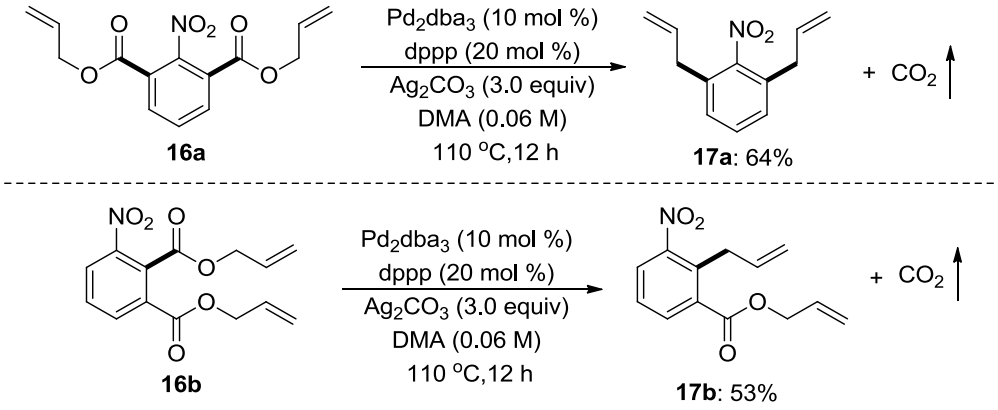



**Scheme 14.** Plausible catalytic cycle for the decarboxylative allylation

## II. 6. The role of nitro group

Finally, to demonstrate the role of the nitro group in decarboxylative allylation, we synthesized diallyl ester **16a** where both ester groups are at *ortho* to the nitro group and its corresponding regioisomer **16b** where one allyl ester group at the *ortho* and other one at the *meta* position. Under slight modified reaction conditions, **16a** afforded diallylation product in good yield via double decarboxylative allylations. Whereas, **16b** afforded the mono-allylation along with the decarboxylative protonation product at the *ortho* position

leaving the *meta* allyl ester intact (Scheme 15). Similarly, *para*-nitro benzoic ester was inactive under the reaction conditions. Presumably, the nitro group at the *ortho* position has a dual role in decarboxylation. First, it can coordinate to either the Ag(I) or Pd(II) prior to and after decarboxylation. This is particularly important for "post-decarboxylation" acting as a C/O bidentate ligand to form a relatively stable 5-membered palladacycle. Secondly, it imparts strong inductive effect that stabilizes the incipient anion which leads to rapid decarboxylation followed by allylation.




**Scheme 15.** Selective decarboxylative allylation of nitro benzoic esters

## II. 7. Conclusion

In conclusion, we have developed a Pd/Ag bimetallic system for the decarboxylative $sp^2$-$sp^3$ allylation of *ortho*-nitrobenzoic esters in intramolecular fashion. A synergistic effect of palladium and silver was observed in this decarboxylative allylation. Mechanistic studies suggest that silver-assisted decarboxylation occurs in an anionic pathway at the present reaction conditions which lead to an allylation product via transmetalation and reductive elimination.

## II. 8. Experimental section

### Preparation of the starting materials

**A. Preparation of allylic ester of 2-nitrobenzoic acids using Steglich's Conditions (13a-14y).**[28] 2-nitrobenzoic acids (1.2 mmol, 1.2 equiv), DMAP ( 0.2 equiv) and DCC (1.2 mmol, 1.2 equiv), were successively added to a solution of respective allyl alcohols

(1.0 mmol, 1.0 equiv) in dry dichloromethane (10 mL) and the resulting mixture was stirred at room temperature until TLC showed complete consumption of the starting materials. Subsequently, the mixture was filtered and concentrated. Purification of the residue by column chromatography (ethyl acetate:hexane, 1:9) afforded the pure product of 2-nitrobenzoic allylic esters.

**B. Preparation of diallylic ester of 2-nitrobenzene-1,3-dioic acid (16a).** 2-nitrobenzene-1,3-dioic acid (1.0 mmol, 1.0 equiv), activated $K_2CO_3$ (16 mmol, 16 equiv) were successively added to a solution of allyl bromide (6 mmol, 6.0 equiv) in dry acetone (15 mL) and the resulting mixture was stirred at room temperature until TLC showed complete consumption of the starting materials. Subsequently, the mixture was filtered and concentrated. Purification of the residue by column chromatography (ethyl acetate:hexane, 1:3) afforded the pure product of 2-nitrobenzeze-1,3-dioic diallylic ester.

**C. Preparation of diallylic ester of 3-nitrobenzene-1,2-dioic acid (16b).** 3-nitrobenzene-1,2-dioic acid (1.0 mmol, 1.0equiv), activated $K_2CO_3$ (16 mmol, 16 equiv) were successively added to a solution of allyl bromide (6 mmol, 6.0 equiv) in dry acetone (15 mL) and the resulting mixture was stirred at room temperature until TLC showed complete consumption of the starting materials. Subsequently, the mixture was filtered and concentrated. Purification of the residue by column chromatography (ethyl acetate:hexane, 1:3) afforded the pure product of diallyl 3-nitrobenzene-1,2-dioate.

**D. Preparation of (*Z*)-but-2-ene-1,4-di-2-nitrobenzoate from 2-nitrobenzoic acid using Steglich's Conditions (15a).**[28] 2-nitrobenzoic acid (1.2 mmol, 2.4 equiv), DMAP ( 0.4 equiv) and DCC (1.2 mmol, 2.4 equiv), were successively added to a solution of (*Z*)-but-2-ene-1,4-diol (0.5 mmol, 1.0 equiv) in dry dichloromethane (10 mL) and the resulting mixture was stirred at room temperature until TLC showed complete consumption of the starting materials. Subsequently, the mixture was filtered and concentrated. Purification of the residue by column chromatography (ethyl acetate:hexane, 1:3) afforded the pure product of 2-nitrobenzoic allylic esters.

**Allyl 2-nitrobenzoate**, **13a, Scheme 9**. Column chromatography ($SiO_2$, eluting with 10:1 hexane/ethyl acetate) afforded the desired product as a pale yellow oil (186 mg, 90%). $^1$H

NMR (600 MHz, $CDCl_3$): $\delta$ 7.90 (dd, $J_1$ = 7.8 Hz, $J_2$ = 1.2 Hz, 1H), 7.75 (dd, $J_1$ = 7.2 Hz, $J_2$ = 1.2 Hz, 1H), 7.67 (dt, $J_1$ = 7.2 Hz, $J_2$ = 1.2 Hz, 1H), 7.63 (dt, $J_1$ = 7.8 Hz, $J_2$ = 1.2 Hz, 1H), 5.94 -6.01 (m, 1H), 5.29-5.40 (m, 2H), 4.81 (d, $J$ = 6.6 Hz, 2H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 165.1, 148.2, 132.9, 131.8, 131.0, 129.9, 127.5, 123.9, 119.4, 67.0; IR (neat): $\upsilon_{max}$ 1737, 1535, 1356, 1290, 1127, 940, 699 cm$^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{10}H_9NO_4Na$ $[M + Na]^+$: 230.0429; found: 230.0466.

**Allyl 4-methoxy-2-nitrobenzoate**, **13b, Scheme 9.** Column chromatography ($SiO_2$, eluting with 6:1 hexane/ethyl acetate) afforded the desired product as a pale yellow oil (206 mg, 87%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.81 (d, $J$ = 8.7 Hz, 1H), 7.24 (d, $J$ = 2.4 Hz, 1H), 7.11 (dd, $J_1$ = 8.7 Hz, $J_2$ = 2.4 Hz, 1H), 5.91-6.04 (m, 1H), 5.28-5.41 (m, 2H), 4.78 (d, $J$ = 6 Hz, 2H), 3.91 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 164.2, 162.4, 150.7, 132.1, 131.3, 119.1, 117.9, 117.4, 109.2, 66.7, 56.2; IR (neat): $\upsilon_{max}$ 1726, 1615, 1543, 1367, 1272, 1124, 1027, 802 cm$^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{11}H_{11}NO_5$ $[M]^+$: 237.0637; found: 237.0614.

**Allyl 4-methyl-2-nitrobenzoate**, **13c, Scheme 9.** Column chromatography ($SiO_2$, eluting with 10:1 hexane/ethyl acetate) afforded the desired product as a pale yellow oil (190 mg, 86%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.68 (d, $J$ = 8.1 Hz, 1H), 7.67 (s, 1H), 7.46 (d, $J$ = 7.5 Hz, 1H), 5.92-6.05 (m, 1H), 5.28-5.42 (m, 2H), 4.80 (d, $J$ = 6 Hz, 2H), 2.48 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 164.9, 148.6, 143.3, 133.1, 131.1, 130.0, 124.2, 119.2, 66.8, 21.3; IR (neat): $\upsilon_{max}$ 1733, 1618, 1538, 1359, 1287, 1131, 840 cm$^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{11}H_{11}NO_4Na$ $[M + Na]^+$: 244.0586; found: 244.0588.

**Allyl 4-bromo-2-nitrobenzoate**, **13d, Scheme 9.** Column chromatography ($SiO_2$, eluting with 10:1 hexane/ethyl acetate) afforded the desired product as a pale yellow oil, (234 mg, 82%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.02 (d, $J$ = 1.8 Hz, 1H), 7.81 (dd, $J_1$ = 8.4 Hz, $J_2$ = 1.8 Hz, 1H), 7.67 (d, $J$ = 8.4 Hz, 1H), 5.91- 6.03 (m, 1H), 5.30 - 5.42 (m, 2H), 4.81 (dd, $J_1$ = 6 Hz, $J_2$ = 1.2 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 164.1, 148.9, 135.8, 131.3, 130.8, 127.0, 125.8, 125.78, 119.7, 67.2; IR (neat): $\upsilon_{max}$ 1735, 1541, 1357, 1283, 1132, 1091 cm$^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{10}H_8BrNO_4Na$ $[M + Na]^+$: 307.9534; found: 307.9679.

**Allyl 4-chloro-2-nitrobenzoate**, **13e, Scheme 9.** Column chromatography ($SiO_2$, eluting with 10:1 hexane/ethyl acetate) afforded the desired product as a colourless oil (200 mg, 83%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.87 (d, $J$ = 1.8 Hz, 1H), 7.76 (d, $J$ = 8.1 Hz, 1H), 7.65 (dd, $J_1$ = 8.4 Hz, $J_2$ = 1.8 Hz, 1H), 5.91- 6.04 (m, 1H), 5.30 -5.43 (m, 2H), 4.82 (d, $J$ = 5.7 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 163.9, 148.9, 138.0, 132.7, 131.2, 130.8, 125.2, 124.1, 119.6, 67.2; IR (neat): $\upsilon_{max}$ 1737, 1603, 1545, 1357, 1278, 1104, 1065, 769 cm$^{-1}$, HRMS (ESI, *m/z*) calcd. for $C_{10}H_8ClNO_4Na$ $[M + Na]^+$: 264.0040; found: 264.0084.

**Allyl 4-phenyl-2-nitrobenzoate**, **13f, Scheme 9**. Column chromatography ($SiO_2$, eluting with 5:1 hexane/ethyl acetate) afforded the desired product as a pale yellow oil (232 mg, 82%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.08 (s, 1H), 7.88 (d, $J$ = 9 Hz, 2H), 7.62 (d, $J$ = 7.5 Hz, 2H), 7.44-7.54 (m, 3H), 5.94-6.07 (m, 1H), 5.31-5.44 (m, 2H), 4.84 (d, $J$ = 5.7 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 164.7, 149.1, 145.4, 137.5, 131.1, 130.7, 130.6 , 129.25, 129.16, 127.1, 125.2, 122.2, 119.3, 66.9; IR (neat): $\upsilon_{max}$ 1731, 1614, 1538, 1360, 1277, 1133, 1073, 762 cm$^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{16}H_{13}NO_4$ $[M]^+$: 283.0845; found: 283.0844.

**Allyl 2-methyl-6-nitrobenzoate**, **13g, Scheme 9.** Column chromatography ($SiO_2$, eluting with 10:1 hexane/ethyl acetate) afforded the desired product as a light yellow oil, (187 mg, 85%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.00 (d, $J$ = 8.1 Hz, 1H), 7.55 (d, $J$ = 7.5 Hz, 1H), 7.47 (dd, $J_1$ = 7.8 Hz, $J_2$ = 7.8 Hz, 1H), 5.99-6.08 (m, 1H), 5.31-5.45 (m, 2H), 4.88 (d, $J$ = 6.0 Hz, 2H), 2.43 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 166.1, 146.2, 137.6, 136.0, 131.3, 129.7, 129.4, 121.8, 119.8, 67.0, 19.1; IR (neat): $\upsilon_{max}$ 1739, 1534, 1349, 1266, 1113, 1073, 804 cm$^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{11}H_{11}NO_4Na$ $[M + Na]^+$: 244.0586; found: 244.0619.

**Allyl 3-methyl-2-nitrobenzoate**, **13h, Scheme 9.** Column chromatography ($SiO_2$, eluting with 10:1 hexane/ethyl acetate) afforded the desired product as a colourless liquid (187 mg, 85%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.88 (dd, $J_1$ = 7.2 Hz, $J_2$ = 1.8 Hz, 1H), 7.43-7.52 (m, 2H), 5.91-6.04 (m, 1H), 5.29-5.43 (m, 2H), 4.79 (dd, $J_1$ = 5.7 Hz, $J_2$ = 0.9 Hz, 2H), 2.36 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 163.2, 150.7, 135.6, 131.1, 130.5,

129.9, 128.8, 123.1, 119.2, 66.7, 17.1; IR (neat): $\upsilon_{max}$ 1722, 1538, 1372, 1285, 1191, 934, 763 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{11}H_{11}NO_4$ $[M]^+$: 221.0688; found: 221.0688.

**Allyl 4,5-dimethoxy-2-nitrobenzoate**, **13i, Scheme 9.** Column chromatography ($SiO_2$, eluting with 5:1 hexane/ethyl acetate) afforded the desired product as a pale yellow oil (219 mg, 82%). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.47 (s, 1H), 7.09 (s, 1H), 5.93-6.04 (m, 1H), 5.30-5.43 (m, 2H), 4.82 (d, $J$ = 6 Hz, 2H), 3.99 (s, 3H), 3.98 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 165.5, 152.4, 150.3, 141.2, 131.2, 121.6, 119.4, 110.7, 106.9, 67.0, 56.6, 56.58; IR (neat): $\upsilon_{max}$ 1722, 1535, 1381, 1287, 1218, 986, 746 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{12}H_{13}NO_6$ $[M]^+$: 267.0743; found: 267.0743.

**Allyl 3,4,5-trimethoxy-2-nitrobenzoate**, **13j, Scheme 9.** Column chromatography ($SiO_2$, eluting with 5:1 hexane/ethyl acetate) afforded the desired product as a colourless solid (237 mg, 80%), m.p. 107 $^oC$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.29 (s, 1H), 5.89-6.02 (m, 1H), 5.29-5.46 (m, 2H), 4.78 (d, $J$ = 5.4 Hz, 2H), 3.96 (s, 9H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 162.5, 154.0, 146.4, 145.7, 130.9, 119.2, 117.7, 108.5, 66.8, 62.6, 61.2, 56.5; IR (neat): $\upsilon_{max}$ 2946, 1724, 1541, 1365, 1339, 1227, 1117, 982, 767 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{13}H_{15}NO_7$ $[M]^+$: 297.0849; found: 297.0839.

**2-Methylallyl 2-nitrobenzoate**, **13k, Scheme 9.** Column chromatography ($SiO_2$, eluting with 10:1 hexane/ethyl acetate) afforded the desired product as a pale yellow oil (183 mg, 83%). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.91 (dd, $J_1$ = 7.8 Hz, $J_2$ = 1.2 Hz, 1H), 7.78 (dd, $J_1$ = 7.2 Hz, $J_2$ = 1.8 Hz, 1H), 7.62-7.72 (m, 2H), 5.05 (s, 1H), 5.00 (s, 1H), 4.75 (s, 2H), 1.81 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 165.0, 148.2, 139.0, 132.8, 131.8, 129.9, 127.4, 123.8, 114.3, 69.8, 19.5; IR (neat): $\upsilon_{max}$ 1736, 1536, 1356, 1293, 1128, 698 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{11}H_{11}NO_4$ $[M]^+$: 221.0688; found: 221.0688.

**2-Methylallyl 3-methyl-2-nitrobenzoate**, **13l, Scheme 9.** Column chromatography ($SiO_2$, eluting with 10:1 hexane/ethyl acetate) afforded the desired product as a light yellow oil (183 mg, 78%). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.89 (dd, $J_1$ = 7.2 Hz, $J_2$ = 1.8 Hz, 1H), 7.44-7.52 (m, 2H), 5.05 (s, 1H), 5.0 (s, 1H), 4.71 (s, 2H), 2.36 (s, 3H), 1.81 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 163.2, 150.6, 139.0, 135.6, 130.5, 129.9, 128.8,

123.1, 114.1, 69.5, 19.5, 17.1; IR(neat): $\upsilon_{max}$ 1730, 1540, 1370, 1284, 1186, 768 $cm^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{12}H_{13}NO_4Na$ $[M + Na]^+$: 258.0742; found: 258.0771.

**2-Methylallyl 4-methoxy-2-nitrobenzoate**, **13m, Scheme 9.** Column chromatography ($SiO_2$, eluting with 5:1 hexane/ethyl acetate) afforded the desired product as a pale yellow oil (216 mg, 86%). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.83 (d, $J$ = 8.7 Hz, 1H), 7.23 (d, $J$ = 2.1 Hz, 1H), 7.11 (dd, $J_1$ = 8.7 Hz, $J_2$ = 2.4 Hz, 1H), 5.03 (s, 1H), 5.0 (s, 1H), 4.70 (s, 2H), 3.91 (s, 3H), 1.80 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 164.1, 162.4, 150.8, 139.2, 132.2, 117.7, 117.3, 114.0, 109.1, 69.5, 56.1, 19.5; IR(neat): $\upsilon_{max}$ 1725, 1617, 1533, 1382, 1328, 1288, 1141, 1023, 845 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{12}H_{13}NO_5$ $[M]^+$: 251.0794; found: 251.0796.

**2-Methylallyl 4,5-dimethoxy-2-nitrobenzoate**, **13n, Scheme 9.** Column chromatography ($SiO_2$, eluting with 5:1 hexane/ethyl acetate) afforded the desired product as a pale yellow oil (230 mg, 82%). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.46 (s, 1H), 7.12 (s, 1H), 5.04 (s, 1H), 4.99 (s, 1H), 4.73 (s, 2H), 3.99 (s, 3H), 3.98 (s, 3H), 1.8 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 165.5, 152.4, 150.4, 141.3, 139.1, 121.4, 114.3, 110.8, 106.9, 69.8, 56.6, 56.57, 19.5; IR (neat): $\upsilon_{max}$ 1731, 1582, 1527, 1347, 1287, 1221, 1052, 757 $cm^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{13}H_{15}NO_6Na$ $[M + Na]^+$: 304.0797; found: 304.0818.

**2-Methylallyl 3,4,5-trimethoxy-2-nitrobenzoate**, **13o, Scheme 9.** Column chromatography ($SiO_2$, eluting with 4:1 hexane/ethyl acetate) afforded the desired product as a pale yellow oil (242 mg, 78%). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.31 (s, 1H), 5.03 (s, 1H), 4.99 (s, 1H), 4.70 (s, 2H), 3.97 (s, 3H), 3.96 (s, 3H), 3.956 (s, 3H), 1.80 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 162.6, 154.0, 146.3, 145.7, 138.9, 117.6, 114.1, 108.6, 69.6, 62.6, 61.2, 56.4, 19.4; IR (neat): $\upsilon_{max}$ 1727, 1658, 1580, 1371, 1341, 1227, 1116, 1026 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{14}H_{17}NO_7$ $[M]^+$: 311.1005; found: 311.1002.

**2-(Methoxycarbonyl)allyl 2-nitrobenzoate**, **13p, Scheme 9.** Column chromatography ($SiO_2$, eluting with 3:1 hexane/ethyl acetate) afforded the desired product as a pale yellow oil (201 mg, 76%). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.92 (dd, $J_1$ = 7.8 Hz, $J_2$ = 1.2 Hz,

1H), 7.77 (dd, $J_1$ = 7.2 Hz, $J_2$ = 1.5 Hz, 1H), 7.58-7.72 (m, 2H), 6.45 (s, 1H), 5.95 (s, 1H), 5.07 (s, 2H), 3.80 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 165.5, 164.8, 148.2, 134.2, 132.9, 132.0, 130.0, 129.1, 127.3, 124.0, 64.4, 52.2; IR (neat): $\upsilon_{max}$ 2932, 1736, 1662, 1531, 1348, 1074, 737 cm$^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{12}H_{11}NO_6$ $[M]^+$: 265.0586; found: 265.0580.

**2-(Methoxycarbonyl)allyl 4-methoxy-2-nitrobenzoate**, **13q, Scheme 9.** Column chromatography ($SiO_2$, eluting with 3:1 hexane/ethyl acetate) afforded the desired product as a pale yellow oil (221 mg, 75%). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 7.78 (d, $J$ = 8.4 Hz, 1H), 7.2 (s, 1H), 7.09 (d, $J$ = 7.8 Hz, 1H), 6.40 (s, 1H), 5.89 (s, 1H), 4.99 (s, 2H), 3.88 (s, 3H), 3.78 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 165.5, 163.8, 162.5, 150.8, 134.3, 132.2, 128.6, 117.4, 117.3, 109.3, 63.94, 56.2, 52.1; IR (neat): $\upsilon_{max}$ 2926, 1726, 1703, 1619, 1527, 1330, 1287, 1137, 1026, 803 cm$^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{13}H_{13}NO_7$ $[M]^+$: 295.0692; found: 295.0693.

**Cinnamyl 4-methoxy-2-nitrobenzoate**, **13r, Scheme 9.** Column chromatography ($SiO_2$, eluting with 5:1 hexane/ethyl acetate) afforded the desired product as a pale yellow oil (263 mg, 84%). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 7.81 (d, $J$ = 9 Hz, 1H), 7.41 (d, $J$ = 7.2 Hz, 2H), 7.33 (t, $J$ = 7.8 Hz, 2H), 7.25-7.28 (m, 1H), 7.24 (d, $J$ = 2.4 Hz, 1H), 7.1 (dd, $J_1$ = 9 Hz, $J_2$ = 3 Hz, 1H), 6.71 (d, $J$ = 16.2 Hz, 1H), 6.31-6.36 (m, 1H), 4.94 (dd, $J_1$ = 6.6 Hz, $J_2$ = 1.2 Hz, 2H), 3.89 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 164.3, 162.3, 150.8, 136.1, 134.9, 132.1, 128.6, 128.2, 126.7, 122.2, 117.9, 117.4, 109.2, 66.6, 56.2; IR (neat): $\upsilon_{max}$ 1726, 1542, 1371, 1280, 1138, 742 cm$^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{17}H_{15}NO_5Na$ $[M + Na]^+$: 336.0848; found: 336.0839.

**Cinnamyl 2-nitrobenzoate**, **13s, Scheme 9.** Column chromatography ($SiO_2$, eluting with 8:1 hexane/ethyl acetate) afforded the desired product as a pale yellow oil (243 mg, 86%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.94 (dd, $J_1$ = 7.8 Hz, $J_2$ = 1.2 Hz, 1H), 7.77 (dd, $J_1$ = 7.5 Hz, $J_2$ = 1.5 Hz, 1H), 7.61-7.71 (m, 2H), 7.42 (d, $J$ = 6.9 Hz, 2H), 7.24-7.36 (m, 3H), 6.73 (d, $J$ = 15.9 Hz, 1H), 6.30-6.40 (m, 1H), 5.0 (dd, $J_1$ = 6.6 Hz, $J_2$ = 1.2 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 165.2, 148.1, 136.0, 135.2, 132.9, 131.8, 129.8, 128.6, 128.2, 127.6, 126.7, 123.9, 121.9, 67.0; IR (neat): $\upsilon_{max}$ 1726, 1531, 1359, 1281, 1132, 1068, 748 cm$^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{16}H_{13}NO_4$ $[M]^+$: 283.0845; found: 283.0850.

**Cinnamyl 3-methyl-2-nitrobenzoate**, **13t, Scheme 9.** Column chromatography ($SiO_2$, eluting with 8:1 hexane/ethyl acetate) afforded the desired product as a colourless liquid (246 mg, 83%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.89 (dd, $J_1$ = 7.2 Hz, $J_2$ = 1.2 Hz, 1H), 7.48-7.52 (m, 2H), 7.41-7.46 (m, 2H), 7.27-7.36 (m, 3H), 6.73 (d, $J$ = 15.9 Hz, 1H), 6.28-6.38 (m, 1H), 4.95 (dd, $J_1$ = 6.6 Hz, $J_2$ = 0.9 Hz, 2H), 2.36 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 163.3, 150.6, 136.0, 135.6, 135.0, 130.4, 129.8, 128.7, 128.6, 128.2, 126.7, 123.12, 121.9, 66.6, 17.0; IR (neat): $\upsilon_{max}$ 1723, 1541, 1374, 1280, 1159, 1123, 725 cm$^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{17}H_{15}NO_4$ $[M]^+$: 297.1001; found: 297.0999.

**Cinnamyl 3,4,5-trimethoxy-2-nitrobenzoate**, **13u, Scheme 9.** Column chromatography ($SiO_2$, eluting with 4:1 hexane/ethyl acetate) afforded the desired product as a colourless solid (291 mg, 78%), m.p. 84 $^o$C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.41-7.43 (m, 2H), 7.30-7.36 (m, 4H), 6.72 (d, $J$ = 15.6 Hz, 1H), 6.26-6.36 (m, 1H), 4.94 (d, $J$ = 6.3 Hz, 2H), 3.97 (s, 3H), 3.96 (s, 3H), 3.95 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 162.5, 153.9, 146.2, 145.6, 140.2, 135.9, 135.0, 128.5, 128.1, 126.6, 121.8, 117.6, 108.4, 66.7, 62.5, 61.1, 56.4; IR (neat): $\upsilon_{max}$ 1724, 1541, 1377, 1340, 1232, 1111, 969 cm$^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{19}H_{19}NO_7Na$ $[M + Na]^+$: 396.1059; found: 396.1037.

**4-Methoxy cinnamyl 4-methoxy-2-nitrobenzoate**, **13v, Scheme 9.** Column chromatography ($SiO_2$, eluting with 4:1 hexane/ethyl acetate) afforded the desired product as a light yellow oil (282 mg, 82%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.81 (d, $J$ = 8.1 Hz, 1H), 7.35 (d, $J$ = 8.7 Hz, 2H), 7.25 (d, $J$ = 2.4 Hz, 1H), 7.11 (dd, $J_1$ = 8.7 Hz, $J_2$ = 2.4 Hz, 1H), 6.86 (d, $J$ = 8.7 Hz, 2H), 6.66 (d, $J$ = 15.9 Hz, 1H), 6.15-6.24 (m, 1H), 4.92 (dd, $J_1$ = 6.6 Hz, $J_2$ = 0.6 Hz, 2H), 3.90 (s, 3H), 3.81 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 164.1, 162.2, 159.5, 150.6, 134.6, 131.9, 128.6, 127.8, 127.5, 119.7, 117.8, 117.2, 113.9, 113.7, 109.1, 66.8, 56.0, 55.1; IR (neat): $\upsilon_{max}$ 1714, 1610, 1540, 1380, 1275, 1126, 1026, 836 cm$^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{18}H_{17}NO_6Na$ $[M + Na]^+$: 366.0954; found: 366.0948.

**4-Methoxycinnamyl 4,5-dimethoxy-2-nitrobenzoate**, **13w, Scheme 9.** Column chromatography ($SiO_2$, eluting with 4:1 hexane/ethyl acetate) afforded the desired product as a light yellow oil (298 mg, 80%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.48 (s, 1H), 7.36 (d, $J$ = 8.4 Hz, 2H), 7.09 (s, 1H), 6.86 (d, $J$ = 8.7 Hz, 2H), 6.68 (d, $J$ = 15.6 Hz, 1H),

6.17-6.27 (m, 1H), 4.95 (d, $J$ = 6.6 Hz, 2H), 3.99 (s, 3H), 3.98 (s, 3H), 3.81 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 165.7, 159.7, 152.5, 150.3, 141.1, 135.0, 128.8, 128.0, 121.9, 119.7, 114.0, 110.7, 106.9, 67.4, 56.64, 56.56, 55.3; IR (neat): $\upsilon_{max}$ 2926, 1721, 1606, 1513, 1384, 1286, 1217, 772 cm$^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{19}H_{19}NO_7$ $[M]^+$: 373.1162; found: 373.1141.

**Allyl benzofuran-2-carboxylate**, **13x, Scheme 10.** Column chromatography ($SiO_2$, eluting with 10:1 hexane/ethyl acetate) afforded the desired product as a colourless liquid (174 mg, 86%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.69 (d, $J$ = 7.8 Hz, 1H), 7.57-7.62 (m, 2H), 7.43 (dt, $J_1$ = 7.2 Hz, $J_2$ = 1.2 Hz, 1H), 7.32 (t, $J_1$ = 7.8 Hz, 1H), 6.12-6.00 (m, 1H), 5.32-5.49 (m, 2H), 4.89 (d, $J$ = 5.7 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 159.2, 155.8, 145.4, 131.6, 127.7, 126.9, 123.8, 122.8, 119.1, 114.1, 112.4, 66.0; IR (neat): $\upsilon_{max}$ 2926, 1730, 1567, 1294, 1177, 749 cm$^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{12}H_{10}O_3Na$ $[M + Na]^+$: 225.0528; found: 225.0536.

**Cinnamyl benzofuran-2-carboxylate**, **13y, Scheme 10.** Column chromatography ($SiO_2$, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a colourless liquid (234 mg, 84%). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 7.69 (d, $J$ = 7.8 Hz, 1H), 7.61 (d, $J$ = 8.4 Hz, 1H), 7.58 (s, 1H), 7.43-7.47 (m, 3H), 7.27-7.36 (m, 4H), 6.78 (d, $J$ = 16.2 Hz, 1H), 6.45-6.40 (m, 1H), 5.05 (d, $J$ = 6.6 Hz, 2H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 159.4, 155.8, 145.4, 136.0, 135.2, 128.6, 128.3, 127.7, 126.9, 126.7, 123.8, 122.9, 122.5, 114.2, 112.4, 66.0; IR (neat): $\upsilon_{max}$ 1724, 1711, 1570, 1447, 1299, 1175, 952, 749 cm$^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{18}H_{14}O_3$ $[M]^+$: 278.0943; found: 278.0934.

**Diallyl 2-nitrobenzene-1,3-dioate**, **16a, Scheme 15.** Column chromatography ($SiO_2$, eluting with 3:1 hexane/ethyl acetate) afforded the desired product as a light yellow oil (221 mg, 76%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.22 (dd, $J_1$ = 8.1 Hz, $J_2$ = 3.9 Hz, 2H), 7.66 (dd, $J_1$ = 7.8 Hz, $J_2$ = 7.8 Hz, 1H), 5.91-6.04 (m, 2H), 5.31-5.44 (m, 4H), 4.81 (d, $J$ = 5.7 Hz, 4H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 162.4, 135.1, 130.7, 130.2, 124.2, 119.6, 67.2; IR (neat): $\upsilon_{max}$ 1737, 1605, 1557, 1261, 1218, 802 cm$^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{14}H_{13}NO_6$ $[M]^+$: 291.0743; found: 291.0742.

**Diallyl 3-nitrobenzene-1,2-dioate**, **16b, Scheme 15**. Column chromatography ($SiO_2$, eluting with 3:1 hexane/ethyl acetate) afforded the desired product as a light yellow oil (209 mg, 72%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.37 (dd, $J_1$ = 8.4 Hz, $J_2$ = 2.4 Hz, 2H), 7.69 (t, $J$ = 8.1 Hz, 1H), 5.94-6.13 (m, 2H), 5.31-5.46 (m, 4H), 4.92 (d, $J$ = 6 Hz, 2H), 4.84 (d, $J$ = 5.7 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 164.9, 163.3, 146.3, 135.7, 131.2, 131.0, 130.8, 130.13, 130.09, 128.2, 119.5, 67.4, 66.9; IR (neat): $\upsilon_{max}$ 1731, 1610, 1540, 1461, 1354, 1269, 1142, 709 cm$^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{14}H_{13}NO_6Na$ $[M + Na]^+$: 314.0641; found: 314.0625.

**(*Z*)-But-2-ene-1,4-di-2-nitrobenzoate**, **15a, Scheme 11**. Column chromatography ($SiO_2$, eluting with 3:1 hexane/ethyl acetate) afforded the desired product as a colourless oil (137 mg, 71%). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 7.92 (d, $J$ = 7.8 Hz, 2H), 7.75 (dd, $J_1$ = 7.8 Hz, $J_2$ = 1.2 Hz, 2H), 7.68 (dt $J_1$ = 7.8 Hz, $J_2$ = 1.2 Hz, 2H), 7.62-7.65 (m, 2H), 5.92 (t, $J$ = 4.2 Hz, 2H), 4.98 (d, $J$ = 5.4 Hz, 4H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 165.1, 148.1, 133.0, 131.8, 129.9, 127.9, 127.5, 123.9, 61.6; IR (neat): $\upsilon_{max}$ 1735, 1534, 1351, 1285, 1254, 1124, 1071, 735 cm$^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{18}H_{14}N_2O_8Na$ $[M + Na]^+$: 409.0648; found: 409.0615.

**General experimental procedure for the decarboxylative allylation of *ortho*-nitrobenzoic esters.**

In a 10 mL two necked round bottom flask equipped with magnetic stir bar was added allyl 2-nitrobenzoate (62.2 mg, 0.30 mmol), silver carbonate (124 mg, 0.45 mmol), dppp (12.4 mg, 0.03 mmol), and $Pd_2(dba)_3$ (13.7 mg, 0.015 mmol). Dimethylacetamide (DMA) 5.0 mL was added into it. The reaction mixture was then evacuated and refilled with nitrogen three times and it was heated at 110 $^o$C under nitrogen atmosphere for 12 hours. After the consumption of the starting materials as indicated by TLC, the reaction mixture was cooled to room temperature, poured into water (25 mL) and extracted with diethyl ether (3 x 25 mL). The combined organic extract was dried (anh. $Na_2SO_4$) and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using pentane eluent. The pure product was isolated as yellow oil in 84% yield (41 mg). Note: This compound is volatile in nature therefore low volatile solvents such as

pentane, diethyl ether were used for column chromatography and medium vacuum was applied for solvent evaporation.

**1-Allyl-2-nitrobenzene**, **14a, Scheme 9.**[22a] Column chromatography ($SiO_2$, eluting with pentane) afforded the desired product as a yellow oil (41 mg, 84%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.92 (dd, $J_1$ = 7.8 Hz, $J_2$ = 0.9 Hz, 1H), 7.54 (t, $J$ = 7.2 Hz, 1H), 7.35-7.39 (m, 2H), 5.91-6.04 (m, 1H), 5.05-5.13 (m, 2H), 3.69 (d, $J$ = 6.3 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 149.3, 135.0, 134.8, 133, 131.9, 127.3, 124.7, 117.1, 36.9.

**1-Allyl-4-methoxy-2-nitrobenzene**, **14b, Scheme 9.** Column chromatography ($SiO_2$, eluting with 95:5 pentane/diethyl ether) afforded the desired product as a yellow oil (49 mg, 85%). $^1$H NMR (600MHz, $CDCl_3$): $\delta$ 7.44 (d, $J$ = 3 Hz, 1H), 7.25 (d, $J$ = 7.8 Hz, 1H), 7.09 (dd, $J_1$ = 8.4 Hz, $J_2$ = 2.4 Hz, 1H), 5.92-5.98 (m, 1H), 5.03-5.09 (m, 2H), 3.85 (s, 3H), 3.62(d, $J$ = 6 Hz, 2H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 158.4, 149.5, 135.5, 132.7, 126.8, 119.8, 116.6, 109.2, 55.8, 36.3; IR (neat): $\upsilon_{max}$ 2933, 1622, 1529, 1251, 1035, 811 cm$^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{10}H_{11}NO_3$ $[M]^+$: 193.0739; found: 193.0714.

**1-Allyl-4-methyl-2-nitrobenzene**, **14c, Scheme 9.** Column chromatography ($SiO_2$, eluting with pentane) afforded the desired product as a yellow oil (40 mg, 75%). $^1$H NMR (300MHz, $CDCl_3$): $\delta$ 7.726 (s, 1H), 7.34 (d, $J$ = 7.5 Hz, 1H), 7.24 (d, $J$ = 7.8 Hz, 1H), 5.89-6.02 (m, 1H), 5.02-5.10 (m, 2H), 3.64 (d, $J$ = 6.3 Hz, 2H), 2.40 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 149.1, 137.6, 135.3, 133.8, 131.8, 131.7, 124.9, 116.8, 36.6, 20.7; IR (neat): $\upsilon_{max}$ 2927, 1636, 1527, 1360, 786 cm$^{-1;}$ HRMS (EI, *m/z*) calcd. for $C_{10}H_{11}NO_2$ $[M]^+$: 177.0790; found: 177.0758.

**1-Allyl-4-bromo-2-nitrobenzene**, **14d, Scheme 9.** Column chromatography ($SiO_2$, eluting with pentane) afforded the desired product as a yellow liquid (48 mg, 67%). $^1$H NMR (300MHz, $CDCl_3$): $\delta$ 8.06 (d, $J$ = 2.1 Hz, 1H), 7.66 (dd, $J_1$ = 8.1 Hz, $J_2$ = 1.8 Hz, 1H), 7.25 (d, $J$ = 8.4 Hz, 1H), 5.86-5.99 (m, 1H), 5.05-5.16 (m, 2H), 3.64 (d, $J$ = 6.3 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 136.0,134.4, 133.9, 133.3, 127.6, 120.2, 117.7, 36.5; IR (neat): $\upsilon_{max}$ 2923, 1637, 1529, 1350, 875 cm$^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_9H_8BrNO_2Na$ $[M + Na]^+$: 263.9636; found: 263.9609.

**1-Allyl-4-chloro-2-nitrobenzene**, **14e, Scheme 9.** Column chromatography ($SiO_2$, eluting with pentane) afforded the desired product as a yellow liquid (32 mg, 54%). $^1$H NMR (600MHz, $CDCl_3$): $\delta$ 7.92 (s, 1H), 7.52 (d, $J$ = 6 Hz, 1H), 7.32 (d, $J$ = 6 Hz, 1H), 5.90-5.97 (m, 1H), 5.07-5.15 (m, 2H), 3.66 (d, $J$ = 6 Hz, 2H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 149.5, 134.4, 133.4, 133.1, 133.0, 132.9, 124.8, 117.6, 36.4; IR (neat): $\upsilon_{max}$ 2923, 1639, 1533, 1352, 1118, 885 cm$^{-1}$; HRMS (EI, *m/z*) calcd. for $C_9H_8ClNO_2$ $[M]^+$: 197.0244; found: 197.0214.

**1-Allyl-4-phenyl-2-nitrobenzene**, **14f, Scheme 9.** Column chromatography ($SiO_2$, eluting with pentane) afforded the desired product as a yellow oil (54 mg, 76%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.15 (d, $J$ = 1.8 Hz, 1H), 7.76 (dd, $J_1$ = 8.1 Hz, $J_2$ = 1.8 Hz, 1H), 7.59-7.65 (m, 2H), 7.39-7.51 (m, 4H), 5.94-6.08 (m, 1H), 5.10-5.16 (m, 2H), 3.73 (d, $J$ = 6.3 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 149.6, 140.8, 138.4, 135.0, 133.5, 132.4, 131.3, 129.1, 128.3, 127.0, 123.0, 117.2, 36.7; IR (KBr): $\upsilon_{max}$ 2923, 1531, 1506, 1350, 761, 696 cm$^{-1}$ ; HRMS (EI, *m/z*) calcd. for $C_{15}H_{13}NO_2$ $[M]^+$: 239.0946; found: 239.0943.

**2-Allyl-1-methyl-3-nitrobenzene**, **14g, Scheme 9.** Column chromatography ($SiO_2$, eluting with pentane) afforded the desired product as a yellow oil (38 mg, 73%). $^1$H NMR (300MHz, $CDCl_3$): $\delta$ 7.62 (d, $J$ = 8.1 Hz, 1H), 7.39 (d, $J$ = 7.2 Hz, 1H), 7.22-7.28 (m, 1H), 5.88-5.99 (m, 1H), 4.92-5.10 (m, 2H), 3.55 (d, $J$ = 5.7 Hz, 2H), 2.40 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 151.1, 139.8, 134.3, 134.2, 131.6, 126.8, 122.0, 116.3, 32.8, 19.8; IR (neat): $\upsilon_{max}$ 2925, 1637, 1527, 1350, 800 cm$^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{10}H_{11}NO_2Na$ $[M + Na]^+$: 200.0687; found: 200.0647.

**1-Allyl-3-methyl-2-nitrobenzene**, **14h, Scheme 9.** Column chromatography ($SiO_2$, eluting with pentane) afforded the desired product as a yellow oil (35 mg, 66%). $^1$H NMR (300MHz, $CDCl_3$): $\delta$ 7.29-7.34 (m, 1H), 7.14-7.17 (m, 2H), 5.82-5.95 (m, 1H), 5.06-5.12 (m, 2H), 3.36 (d, $J$ = 6.6 Hz, 2H), 2.32 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 151.5, 134.8, 131.3, 130.1, 129.6, 129.3, 128.2, 117.3, 35.5, 17.4; IR (neat): $\upsilon_{max}$ 2923, 1639, 1527, 1369, 1217, 757 cm$^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{10}H_{11}NO_2Na$ $[M + Na]^+$: 200.0687; found: 200.0677.

**1-Allyl-4,5-dimethoxy-2-nitrobenzene**, **14i, Scheme 9.** Column chromatography ($SiO_2$, eluting with 95:5 pentane/diethyl ether) afforded the desired product as a yellow oil (54 mg, 80%). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 7.60 (s, 1H), 6.74 (s, 1H), 5.95-6.02 (m, 1H), 5.06-5.12 (m, 2H), 3.95 (s, 3H), 3.93 (s, 3H), 3.71 (d, $J$ = 6.6 Hz, 2H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 153.0, 147.3, 141.1, 135.4, 130.2, 116.8, 113.0, 108.1, 56.3, 37.5; IR (KBr): $\upsilon_{max}$ 2965, 1577, 1519, 1263, 1059, 796 cm$^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{11}H_{13}NO_4$ $[M]^+$: 223.0845; found: 223.0847.

**1-Allyl-3,4,5-trimethoxy-2-nitrobenzene**, **14j, Scheme 9.** Column chromatography ($SiO_2$, eluting with 95:5 pentane/diethyl ether) afforded the desired product as a yellow oil (40 mg, 53%). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 6.51 (s, 1H), 5.84-5.90 (m, 1H), 5.09-5.13 (m, 2H), 3.97 (s, 3H), 3.89 (s, 3H), 3.87 (s, 3H), 3.33 (d, $J$ = 6.6 Hz, 2H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 154.9, 146.1, 140.8, 139.8, 134.5, 127.9, 117.6, 107.6, 62.3, 61.1, 56.2, 35.5; IR (KBr): $\upsilon_{max}$ 2943, 1579, 1528, 1342, 1118, 800 cm$^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{12}H_{15}NO_5$ $[M]^+$: 253.0950; found: 253.0949.

**1-(2-Methylallyl)-2-nitrobenzene**, **14k, Scheme 9.** Column chromatography ($SiO_2$, eluting with pentane) afforded the desired product as a yellow oil (43 mg, 81%). $^1$H NMR (600 MHz, CDCl3): $\delta$ 7.89 (dd, $J_1$ = 7.8 Hz, $J_2$ = 1.8 Hz, 1H), 7.5 (dt, $J_1$ = 7.8 Hz, $J_2$ = 1.2 Hz, 1H), 7.35-7.39 (m, 2H), 4.84 (s, 1H), 4.51 (s, 1H), 3.64 (s, 2H), 1.74 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 149.7, 143.1, 134.3, 132.7, 132.3, 127.4, 124.6, 112.5, 40.4, 22.7; IR (neat): $\upsilon_{max}$ 2916, 1650, 1608, 1525, 1348, 734 cm$^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{10}H_{11}NO_2Na$ $[M + Na]^+$: 200.0687; found: 200.0667.

**1-Methyl-3-(2-methylallyl)-2-nitrobenzene**, **14l, Scheme 9.** Column chromatography ($SiO_2$, eluting with pentane) afforded the desired product as a yellow oil (33 mg, 57%). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 7.31 (t, $J$ = 7.2 Hz, 1H), 7.16 (t, $J$ = 7.2 Hz, 2H), 4.86 (s, 1H), 4.68 (s, 1H), 3.32 (s, 2H), 2.32 (s, 3H), 1.68 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 151.9, 142.5, 130.9, 129.9, 129.5, 129.4, 128.5, 113.4, 39.4, 22.1, 17.4; IR (neat): $\upsilon_{max}$ 2925, 1652, 1529, 1369, 783 cm$^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{11}H_{13}NO_2Na$ $[M + Na]^+$: 214.0844; found: 214.0821.

**4-Methoxy-1-(2-methylallyl)-2-nitrobenzene**, **14m, Scheme 9.** Column chromatography ($SiO_2$, eluting with 98:2 pentane/acetone) afforded the desired product as a yellow oil (53 mg, 85%). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 7.42 (d, $J$ = 2.4 Hz, 1H), 7.23 (d, $J$ = 8.4 Hz, 1H), 7.08 (dd, $J_1$ = 8.4 Hz, $J_2$ = 3 Hz, 1H), 4.80 (s, 1H), 4.49(s, 1H), 3.85 (s, 3H), 3.56 (s, 2H), 1.73 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 158.4, 149.9, 143.5, 133.1, 126.2, 119.5, 112.1, 109.2, 55.7, 39.8, 22.7; IR (neat): $\upsilon_{max}$ 1649, 1530, 1353, 1251, 1037, 771 cm$^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{11}H_{13}NO_3$ $[M]^+$: 207.0895; found: 207.0881.

**1,2-Dimethoxy-4-(2-methylallyl)-5-nitrobenzene**, **14n, Scheme 9.** Column chromatography ($SiO_2$, eluting with 98:2 pentane/acetone) afforded the desired product as a yellow oil (53 mg, 74%). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 7.60 (s, 1H), 6.73 (s, 1H), 4.82 (s, 1H), 4.48 (s, 1H), 3.94(s, 3H), 3.93 (s, 3H), 3.66 (s, 2H), 1.77 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 152.8, 147.3, 143.6, 141.5, 129.7, 113.5, 111.9, 108.1, 56.29, 56.28, 40.9, 22.9; IR (neat): $\upsilon_{max}$ 1649, 1580, 1521, 1329, 1269, 1063, 883 cm$^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{12}H_{15}NO_4$ $[M]^+$: 237.1001; found: 237.1004.

**1,2,3-Trimethoxy-5-(2-methylallyl)-4-nitrobenzene**, **14o, Scheme 9.** Column chromatography ($SiO_2$, eluting with 97:3 pentane/acetone) afforded the desired product as a yellow oil (41 mg, 52%). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 6.52 (s, 1H), 4.87 (s, 1H), 4.71 (s, 1H), 3.97 (s, 3H), 3.92 (s, 3H), 3.88 (s, 3H), 3.28 (s, 2H), 1.69 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 154.7, 146.0, 142.4, 140.8, 140.2, 127.4, 113.5, 107.8, 62.3, 61.1, 56.2, 39.4, 22.1; IR (neat): $\upsilon_{max}$ 2941, 1650, 1577, 1529, 1116, 1027, 800 cm$^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{13}H_{17}NO_5$ $[M]^+$: 267.1107; found: 267.1085.

**Methyl 2-(2-nitrobenzyl)acrylate**, **14p, Scheme 9.**[29] Column chromatography ($SiO_2$, eluting with 9:1 pentane/diethyl ether) afforded the desired product as a yellow oil (48 mg, 73%). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 7.94 (dd, $J_1$ = 8.4 Hz, $J_2$ = 1.2 Hz, 1H), 7.54 (dt, $J_1$ = 7.8 Hz, $J_2$ = 1.2 Hz , 1H), 7.36-7.41 (m, 2H), 6.27 (s, 1H), 5.40 (s, 1H), 3.96 (s, 2H), 3.74 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 166.8, 149.4, 138.0, 133.5, 133.0, 132.4, 127.7, 127.0, 124.9, 52.1, 34.8.

**Methyl 2-(4-methoxy-2-nitrobenzyl)acrylate**, **14q, Scheme 9.** Column chromatography ($SiO_2$, eluting with 97:3 pentane/acetone) afforded the desired product as a yellow oil (57 mg, 75%). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 7.46 (d, $J$ = 3 Hz, 1H), 7.25 (d, $J$ = 8.4 Hz, 1H), 7.09 (dd, $J_1$ = 8.4 Hz, $J_2$ = 2.4 Hz, 1H), 6.23 (d, $J$ = 0.6 Hz, 1H), 5.37 (d, $J$ = 1.2 Hz, 1H), 3.90 (s, 2H), 3.85 (s, 3H), 3.73 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 166.9, 158.6, 149.7, 138.4, 133.3, 126.5, 125.3, 119.7, 109.4, 55.8, 52.0, 34.2; IR (neat): $\upsilon_{max}$ 2952, 1720, 1623, 1529, 1137, 815 cm$^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{12}H_{13}NO_5$ [M + Na]$^+$: 251.0794; found: 251.0793.

**1-((*E*)-3-(4-Methoxy-2-nitrophenyl)prop-1-enyl)benzene**, **14r, Scheme 9.** Column chromatography ($SiO_2$, eluting with 97:3 hexane/ethyl acetate) afforded the desired product as a yellow oil (70 mg, 87%). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 7.47 (d, $J$ = 3 Hz, 1H), 7.35-7.31 (m, 3H), 7.30-7.28 (m, 2H), 7.21 (t, $J$ = 7.2 Hz, 1H), 7.10 (dd, $J_1$ = 8.4 Hz, $J_2$ = 3 Hz, 1H), 6.45 (d, $J$ = 15.6 Hz, 1H), 6.31-6.36 (m, 1H), 3.86 (s, 3H), 3.77 (dd, $J_1$ = 7.2 Hz, $J_2$ = 0.6 Hz, 2H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 158.4, 149.5, 137.1, 132.8, 131.9, 128.5, 127.3, 127.2, 127.1, 126.2, 120.0, 109.2, 55.8, 35.6; IR (neat): $\upsilon_{max}$ 2977, 1636, 1577, 1532, 1323, 744, 805 cm$^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{16}H_{15}NO_3Na$ [M + Na]$^+$: 292.0950; found: 292.0931.

**1-((*E*)-3-(2-Nitrophenyl)prop-1-enyl)benzene**, **14s, Scheme 9.** Column chromatography ($SiO_2$, eluting with 99:1 hexane/ethyl acetate) afforded the desired product as a yellow oil (62 mg, 86%). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 7.95 (dd, $J_1$ = 8.4 Hz, $J_2$ = 1.2 Hz, 1H), 7.55 (dt, $J_1$ = 7.2 Hz, $J_2$ = 1.2 Hz, 1H), 7.44 (dd, $J_1$ = 7.8 Hz, $J_2$ = 1.2 Hz, 1H), 7.39 (dt, $J_1$ = 8.4 Hz, $J_2$ = 1.2 Hz, 1H), 7.35-7.36 (m, 2H), 7.28-7.31 (m, 2H), 7.22 (tt, $J_1$ = 7.2 Hz, $J_2$ = 1.2 Hz, 1H), 6.49 (d, $J$ = 15.6 Hz, 1H), 6.33-6.38 (m, 1H), 3.84 (dd, $J_1$ = 6.6 Hz, $J_2$ = 1.2 Hz, 2H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 149.2, 137.0, 135.2, 133.1, 132.4, 131.9, 128.5, 127.4, 127.3, 126.7, 126.2, 124.8, 36.2; IR (neat): $\upsilon_{max}$ 1724, 1604, 1525, 1344, 970, 738 cm$^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{15}H_{13}NO_2$ [M]$^+$: 239.0946; found: 239.0948.

**1-((*E*)-3-(3-Methyl-2-nitrophenyl)prop-1-enyl)benzene**, **14t, Scheme 9.** Column chromatography ($SiO_2$, eluting with 99:1 hexane/ethyl acetate) afforded the desired product as a yellow oil (45 mg, 60%). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 7.34-7.36 (m, 2H),

7.28-7.33 (m, 3H), 7.20-7.23 (m, 2H), 7.17 (d, *J* = 7.8 Hz, 1H), 6.46 (d, *J* = 15.6 Hz, 1H), 6.23-6.28 (m, 1H), 3.51 (dd, $J_1$ = 7.2 Hz, $J_2$ = 1.2 Hz, 2H), 2.34 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 151.5, 136.9, 132.4, 131.6, 130.2, 129.7, 129.4, 128.5, 128.2, 127.4, 126.4, 126.2, 34.7, 17.4; IR (neat): $\upsilon_{max}$ 1577, 1525, 1368, 966, 851 cm$^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{16}H_{15}NO_2$ $[M]^+$: 253.1103; found: 253.1101.

**1-((*E*)-3-(3,4,5-Trimethoxy-2-nitrophenyl)prop-1-enyl)benzene**, **14u, Scheme 9.** Column chromatography ($SiO_2$, eluting with 97:3 hexane/acetone) afforded the desired product as a yellow oil (49 mg, 50%). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.35-7.41 (m, 2H), 7.29-7.32 (m, 2H), 7.21-7.24 (m, 1H), 6.56 (s, 1H), 6.48 (d, *J* = 15.5 Hz, 1H), 6.21-6.27 (m, 1H), 3.98 (s, 3H), 3.88 (s, 6H), 3.48 (d, *J* = 6.5 Hz, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$):$\delta$ 155.1, 146.3, 141.1, 140.0, 137.0, 132.7, 128.9, 128.7, 128.3, 127.7, 126.4, 126.3, 107.9, 62.4, 61.2, 56.4, 35.0; IR(neat): $\upsilon_{max}$ 2941, 1579, 1529, 1365, 1116, 754 cm$^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{18}H_{19}NO_5$ $[M]^+$: 329.1263; found: 329.1263.

**1-Methoxy-4-((*E*)-3-(4-methoxy-2-nitrophenyl)prop-1-enyl)benzene**, **14v, Scheme 9.** Column chromatography ($SiO_2$, eluting with 97:3 hexane/acetone) afforded the desired product as a yellow oil (79 mg, 88%). $^1$H NMR (600MHz, $CDCl_3$): $\delta$ 7.46 (d, *J* = 2.4 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.09 (dd, $J_1$ = 8.4 Hz, $J_2$ = 2.4 Hz, 1H), 6.83 (d, *J* = 9 Hz, 2H), 6.39 (d, *J* = 16.2 Hz, 1H), 6.17-6.21 (m, 1H), 3.86 (s, 3H), 3.80 (s, 3H), 3.74 (d, *J* = 6.6 Hz, 2H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 159.0, 158.4, 149.4, 132.8, 131.3, 129.9, 127.4, 127.3, 124.9, 119.9, 113.9, 109.2, 55.8, 55.3, 35.6; IR (neat): $\upsilon_{max}$ 2970, 1606, 1510, 1251, 1029, 842 cm$^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{17}H_{17}NO_4Na$ $[M + Na]^+$: 322.1055; found: 322.1108.

**1-Methoxy-4-((*E*)-3-(4,5-dimethoxy-2-nitrophenyl)prop-1-enyl)benzene**, **14w, Scheme 9.** Column chromatography ($SiO_2$, eluting with 97:3 hexane/acetone) afforded the desired product as a yellow oil (84 mg, 85%). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 7.63 (s, 1H), 7.28 (d, *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 8.4 Hz, 2H), 6.79 (s, 1H), 6.42 (d, *J* = 16.2 Hz, 1H), 6.20-6.24 (m, 1H), 3.94 (s, 3H), 3.93 (s, 3H), 3.84 (d, *J* = 6.6 Hz, 2H), 3.79 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 159.0, 153.1, 147.3, 141.0, 131.3, 130.8, 129.9, 127.3, 124.8, 113.9, 113.1, 108.2, 56.33, 56.30, 55.26, 36.9; IR (neat): $\upsilon_{max}$ 1606, 1579, 1519,

1328, 1267, 1054, 796 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{18}H_{19}NO_5$ $[M]^+$: 329.1263; found: 329.1264.

**2-Allylbenzofuran**, **14x, Scheme 10.**[30] Column chromatography ($SiO_2$, eluting with pentane) afforded the desired product as a colourless oil (26 mg, 53%). $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 7.48-7.50 (m, 1H), 7.42-7.43 (m, 1H), 7.17-7.23 (m, 2H), 6.43 (d, $J$ = 1.2 Hz, 1H), 5.99-6.06 (m, 1H), 5.24 (dq, $J_1$ = 17.1 Hz, $J_2$ = 1.8 Hz, 1H), 5.19 (dq, $J_1$ = 9.9 Hz, $J_2$ = 1.2 Hz, 1H), 3.55 (dd, $J_1$ = 6.6 Hz, $J_2$ = 1.2 Hz, 2H); $^{13}C$ NMR (150 MHz, $CDCl_3$): $\delta$ 157.0, 154.8, 133.1, 128.8, 123.3, 122.5, 120.3, 117.6, 110.8, 102.6, 33.0.

**2-Cinnamylbenzofuran**, **14y, Scheme 10.**[31] Column chromatography ($SiO_2$, eluting with pentane) afforded the desired product as a colourless oil (42 mg, 60%). $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 7.49-7.51 (m, 1H), 7.43-7.44 (m, 1H), 7.39-7.40 (m, 2H), 7.31-7.33 (m, 2H), 7.22-7.25 (m, 2H), 7.19 (dt, $J_1$ = 7.8 Hz, $J_2$ = 1.2 Hz, 1H), 6.58 (d, $J$ = 16.2 Hz, 1H), 6.48 (d, $J$ = 0.6 Hz, 1H), 6.37-6.42 (m, 1H), 3.71 (d, $J$ = 7.2 Hz, 2H); $^{13}C$ NMR (150 MHz, $CDCl_3$): $\delta$ 157.1, 154.8, 137.0, 132.7, 128.8, 128.5, 127.4, 126.2, 124.6, 123.4, 122.5, 120.4, 110.8, 102.7, 32.2; IR (neat): $\upsilon_{max}$ 2925, 1600, 1454, 1253, 964, 750 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{17}H_{14}O$ $[M]^+$: 234.1045; found: 234.1048.

**1,3-Diallyl-2-nitrobenzene**, **17a, Scheme 15.** Column chromatography ($SiO_2$, eluting with pentane) afforded the desired product as a yellow oil (39 mg, 64%). $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 7.36 (t, $J$ = 7.8 Hz, 1H), 7.19 (d, $J$ = 7.8 Hz, 2H), 5.85-5.92 (m, 2H), 5.08-5.13 (m, 4H), 3.36 (d, $J$ = 6.6 Hz, 4H); $^{13}C$ NMR (150 MHz, $CDCl_3$): $\delta$ 151.1, 134.7, 131.5, 130.3, 128.7, 117.4, 35.5; IR (neat): $\upsilon_{max}$ 2923, 1639, 1529, 1369, 1218, 921, 757 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{12}H_{13}NO_2$ $[M]^+$: 203.0946; found: 203.0940.

**Allyl 2-allyl-3-nitrobenzoate**, **17b, Scheme 15.** Column chromatography ($SiO_2$, eluting with 95:5 pentane/diethyl ether) afforded the desired product as a yellow oil (39 mg, 53%). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 8.00 (dd, $J_1$ = 7.8 Hz, $J_2$ = 0.9 Hz, 1H), 7.83 (dd, $J_1$ = 8.1 Hz, $J_2$ = 0.9 Hz, 1H), 7.44 (t, $J$ = 8.1 Hz, 1H), 5.86-6.09 (m, 2H), 5.31-5.45 (m, 2H), 4.94-5.06 (m, 2H), 4.82 (d, $J$ = 6 Hz, 2H), 3.90 (d, $J$ = 6 Hz, 2H); $^{13}C$ NMR (75 MHz, CDCl3): $\delta$ 166.1, 151.8, 134.9, 133.9, 133.6, 133.4, 131.4, 127.1, 126.9, 119.3,

116.7, 66.4, 32.0; IR (KBr): $\upsilon_{max}$ 1728, 1533, 1446, 1359, 1259, 1122, 921, 744 $cm^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{13}H_{13}NO_4Na$ $[M + Na]^+$: 270.0742; found: 270.0728.

**Experimental procedure for diene formation via β-hydride elimination of diallyl ester 15a.**

In a 10 mL two necked round bottom flask equipped with magnetic stir bar was added (*Z*)-But-2-ene-1,4-di-2-nitrobenzoate (116 mg, 0.30 mmol), silver carbonate (248 mg, 0.9 mmol), dppp (24.8 mg, 0.06 mmol), and $Pd_2(dba)_3$ (27.4 mg, 0.03 mmol). Dimethylacetamide (DMA) 5 ml was added into it. The reaction mixture was then evacuated and refilled with nitrogen three times and it was heated at 110 $^oC$ under nitrogen atmosphere for 12 hours. After the consumption of the starting materials as indicated by TLC, the reaction mixture was cooled to room temperature, poured into water (25 mL) and extracted with diethyl ether (3 × 25 mL). The combined organic extract was dried (anh. $Na_2SO_4$) and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using pentane eluent. The pure product was isolated as yellow solid in 43% yield (23 mg).

**1-((*E*)-Buta-1,3-dienyl)-2-nitrobenzene**, **15b, Scheme 11.**[32] $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.91 (d, $J$ = 8.1 Hz, 1H), 7.67 (d, $J$ = 7.8 Hz, 1H), 7.56 (t, $J$ = 7.5 Hz, 1H), 7.37 (t, $J$ = 7.2 Hz, 1H), 7.05 (d, $J$ = 15.6 Hz, 1H), 6.78 (dd, $J_1$ = 15.3 Hz, $J_2$ = 10.5 Hz, 1H), 6.50-6.63 (m, 1H), 5.44 (d, J = 16.8 Hz, 1H), 5.32 (d, J = 9.6 Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 148.05, 136.7, 134.6, 132.8, 132.6, 127.94, 127.9, 127.2, 124.7, 120.3.

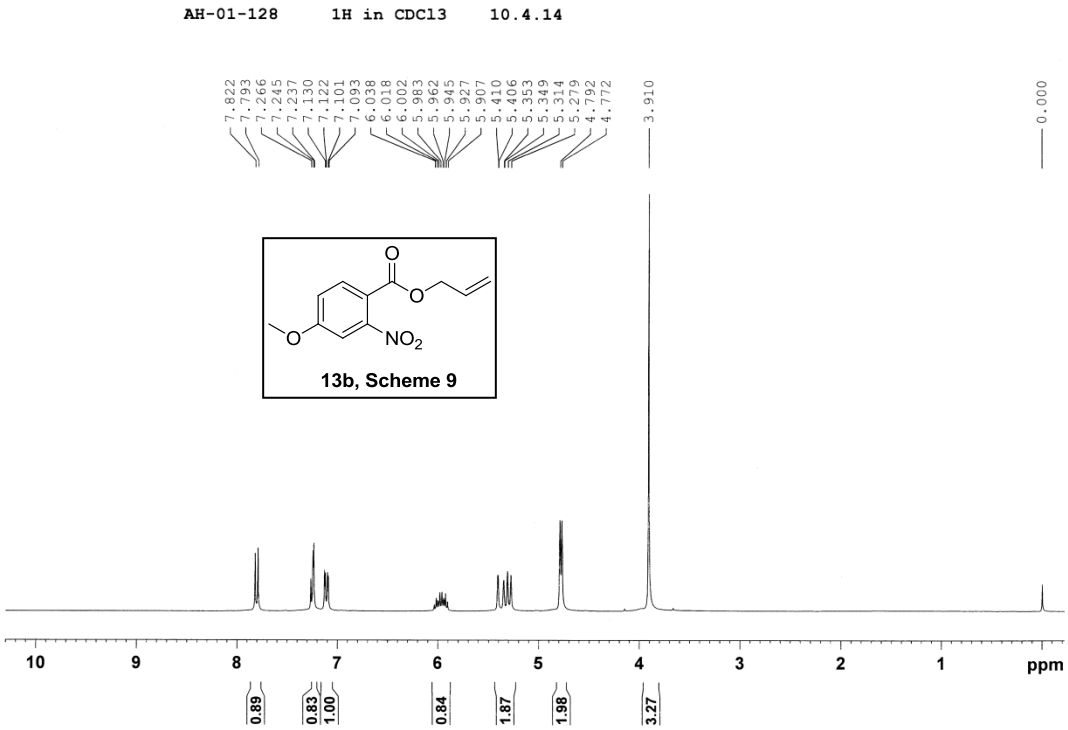
**General experimental procedure for reduction of allyl nitro compounds.**[33]

Sodium borohydride (40 mg, 1 mmol) was added to a stirring solution of ferrous sulphatehepta-hydrate [$FeSO_4$, $7H_2O$] (167 mg, 0.6 mmol) and citric acid (11mg, 0.05 mmol) in water (20 mL) and vigorous stirring was continued for 3-4 minutes. When the solution settled down the water layer was decanted. The residual black solid material of Fe nanoparticles was further washed with water two times to be ready for use in nitro reduction. The 1-allyl-2-nitrobenzene compound (0.2 mmol) was added to these Fe nanoparticles in water (3 mL) in the same pot under constant stirring at room temperature under argon. After completion of reaction (TLC) the mixture was extracted with diethyl

ether (3 x 10 mL) (all Fe-species remained around stirring bar). Evaporation of solvent and purification by column chromatography ($SiO_2$, eluting with 94:6 pentane/diethyl ether) afforded the desired product as a yellow oil, (23 mg, 86%).

**2-Allylbenzenamine**, **18a.**[34] $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.04-7.13 (m, 2H), 6.75 (t, $J$ = 7.2 Hz, 1H), 6.68 (d, $J$ = 7.8 Hz, 1H), 5.89-6.02 (m, 1H), 5.07-5.14 (m, 2H), 3.68 (br s, 2H), 3.31 (d, $J$ = 6.3 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 144.8, 135.9, 130.2, 127.5, 124.0, 118.9, 116.1, 115.8, 36.5.

## II. 9. $^1$H and $^{13}$C Spectra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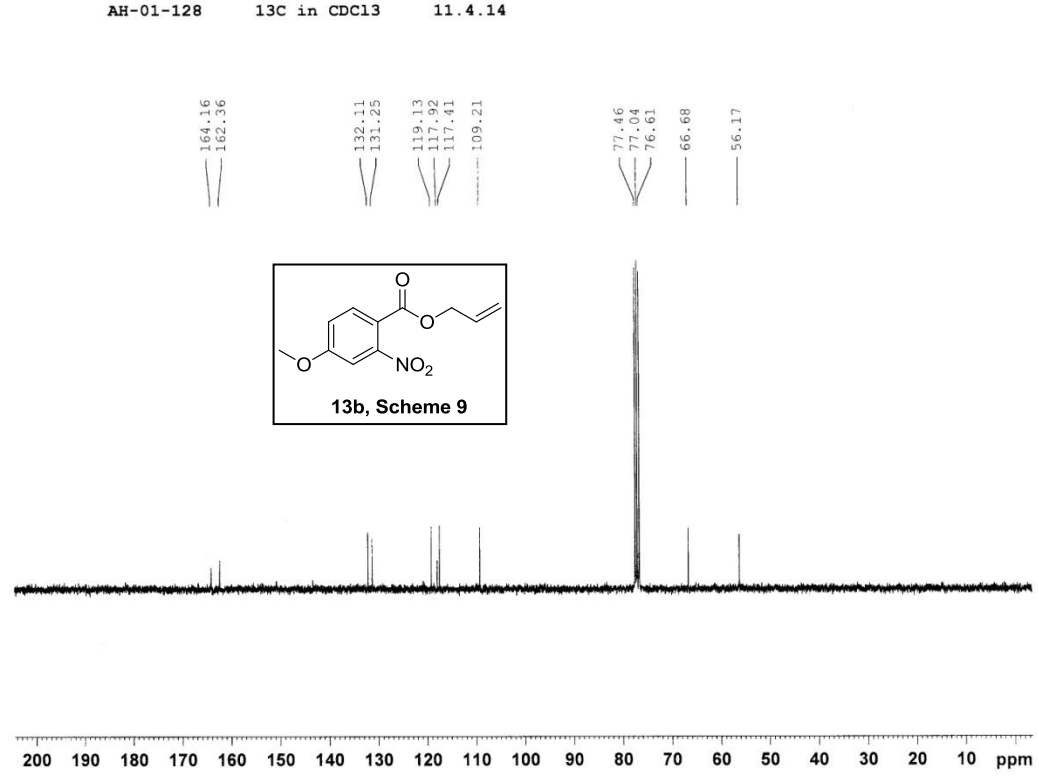
7.793
7.266
7.245
7.237
7.130
7.122
7.101
7.093
6.038
6.018
6.002
5.983
5.962
5.945
5.927
5.907
5.410
5.406
5.353
5.349
5.314
5.279
4.792
4.772
3.910
0.000
13b, Scheme 9
10
9
8
7
6
5
4
3
2
1
ppm
0.89
0.83
1.00
0.84
1.87
1.98
3.27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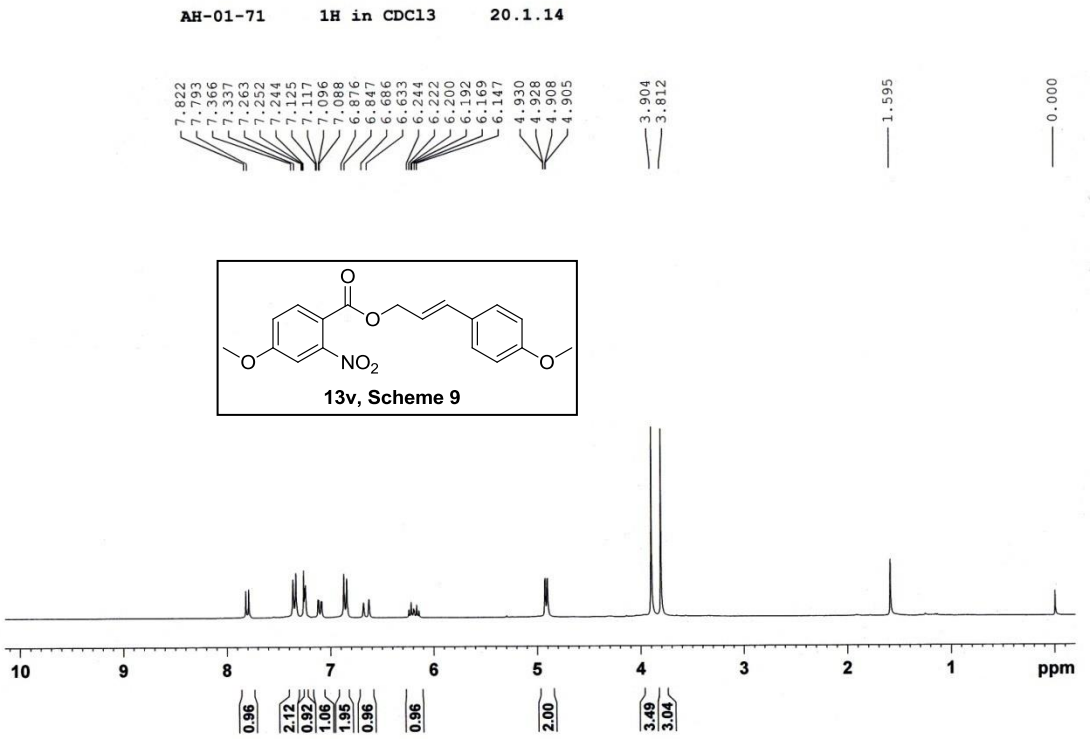
162.36
132.11
131.25
119.13
117.92
117.41
109.21
77.46
77.04
76.61
66.68
56.17
13b, Scheme 9
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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7.252
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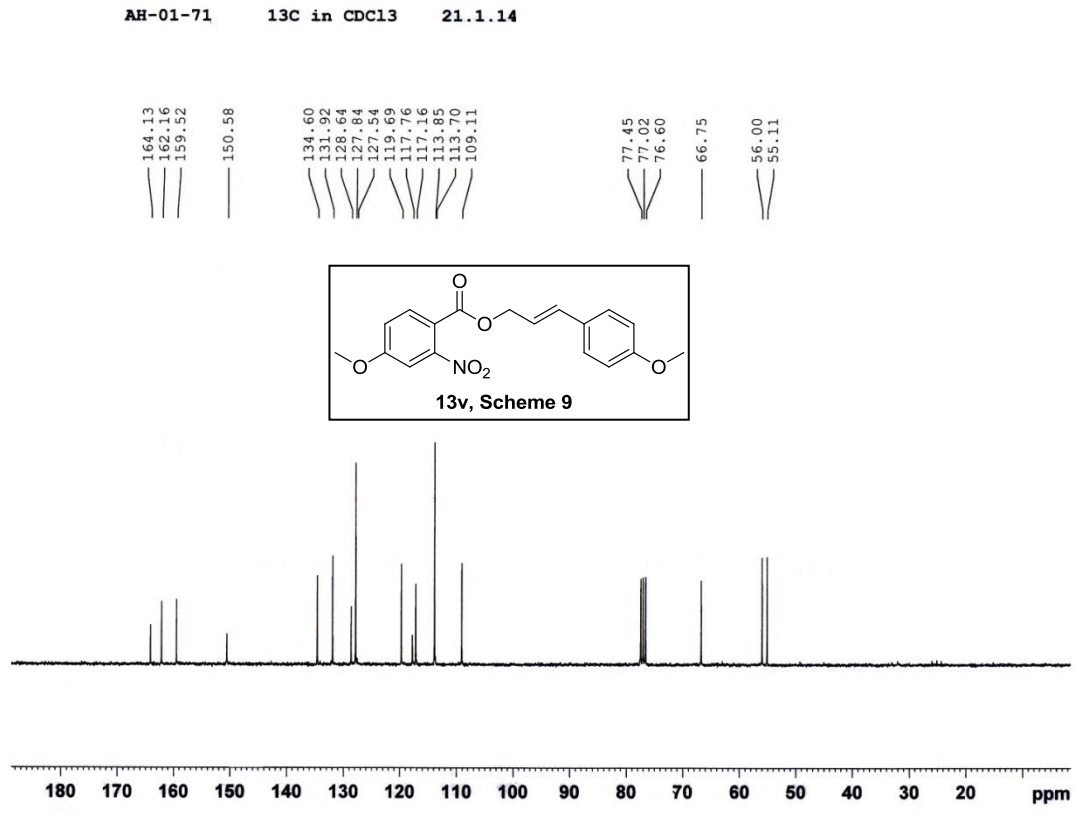
7.117
7.096
7.088
6.876
6.847
6.686
6.633
6.244
6.222
6.200
6.192
6.169
6.147
4.930
4.928
4.908
4.905
3.904
3.812
1.595
0.000
13v, Scheme 9
10
9
8
7
6
5
4
3
2
1
ppm
0.96
2.12
0.92
1.06
1.95
0.96
0.96
2.00
3.49
3.04


AH-01-71 13C in CDCl3 21.1.14
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162.16
159.52
150.58
134.60
131.92
128.64
127.84
127.54
119.69
117.76
117.16
113.85
113.70
109.11
77.45
77.02
76.60
66.75
56.00
55.11
13v, Scheme 9
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160
150
140
130
120
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80
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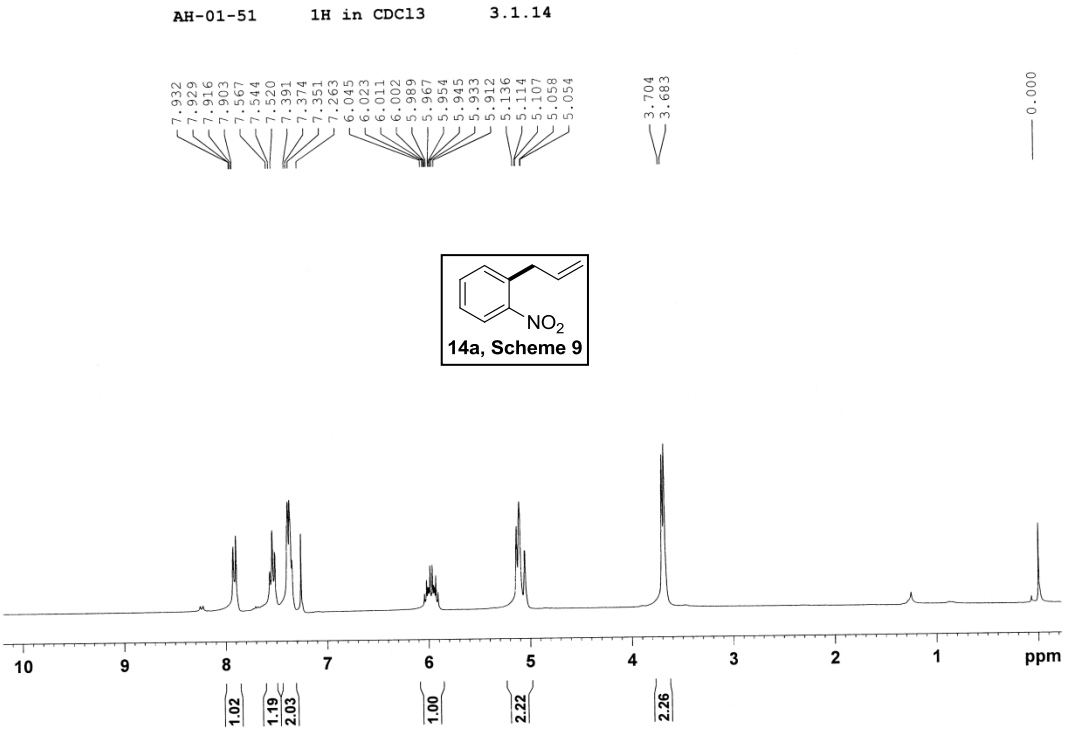
50
40
30
20
ppm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7.929
7.916
7.903
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7.520
7.391
7.374
7.351
7.263
6.045
6.023
6.011
6.002
5.989
5.967
5.954
5.945
5.933
5.912
5.136
5.114
5.107
5.058
5.054
3.704
3.683
0.000
NO2
14a, Scheme 9
10
9
8
7
6
5
4
3
2
1
ppm
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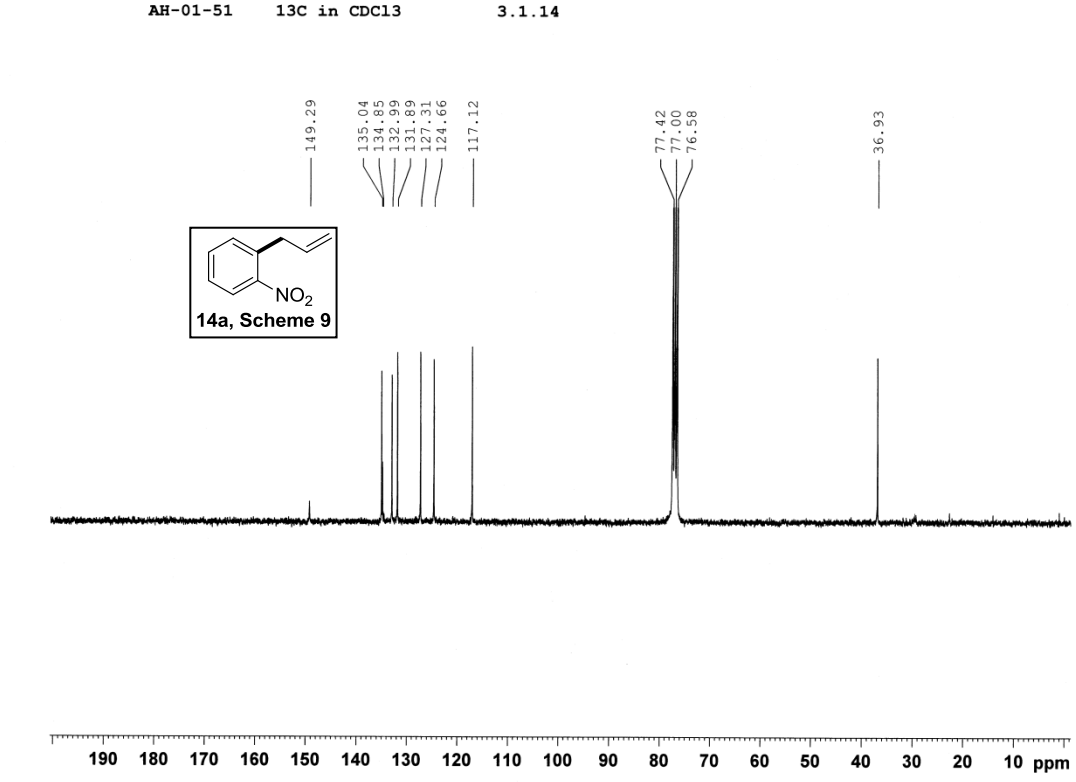
1.19
2.03
1.00
2.22
2.26


AH-01-51 13C in CDCl3 3.1.14
149.29
135.04
134.85
132.99
131.89
127.31
124.66
117.12
77.42
77.00
76.58
36.93
NO2
14a, Scheme 9
190
180
170
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150
140
130
120
110
100
90
80
70
60
50
40
30
20
10 ppm

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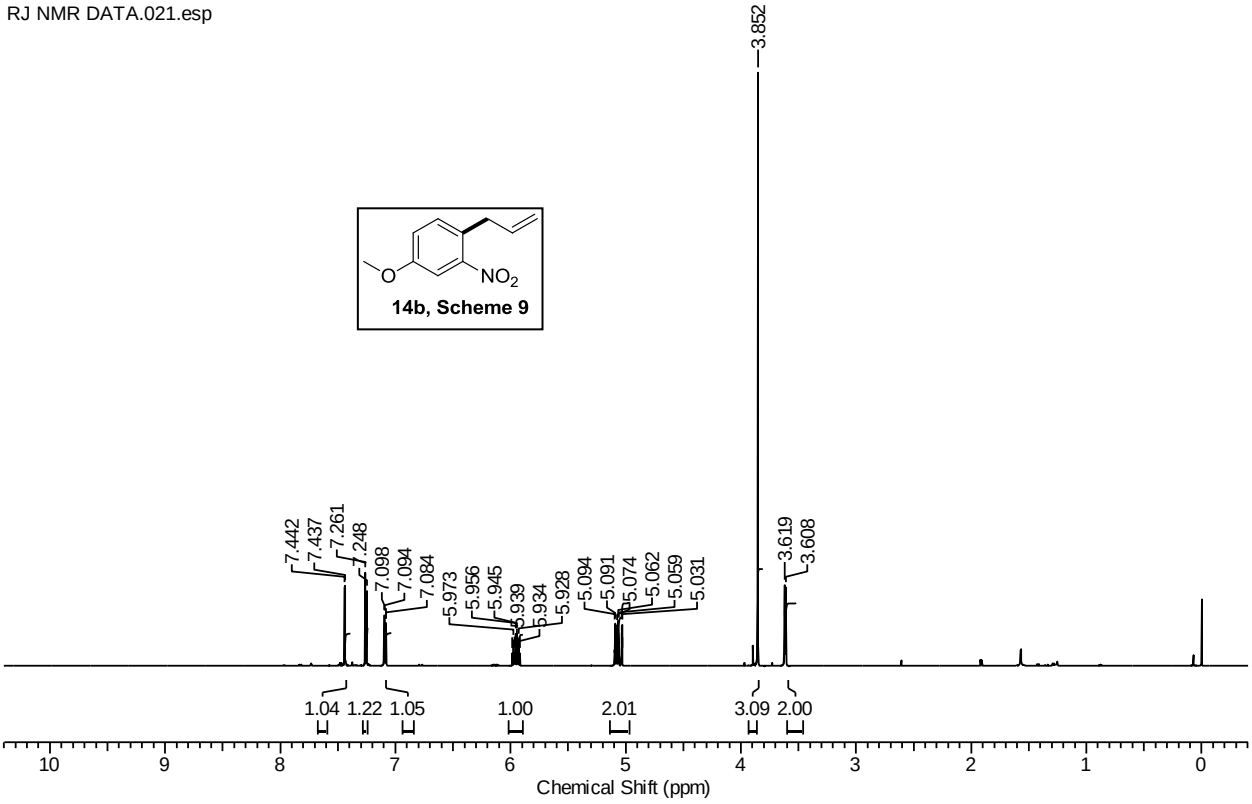


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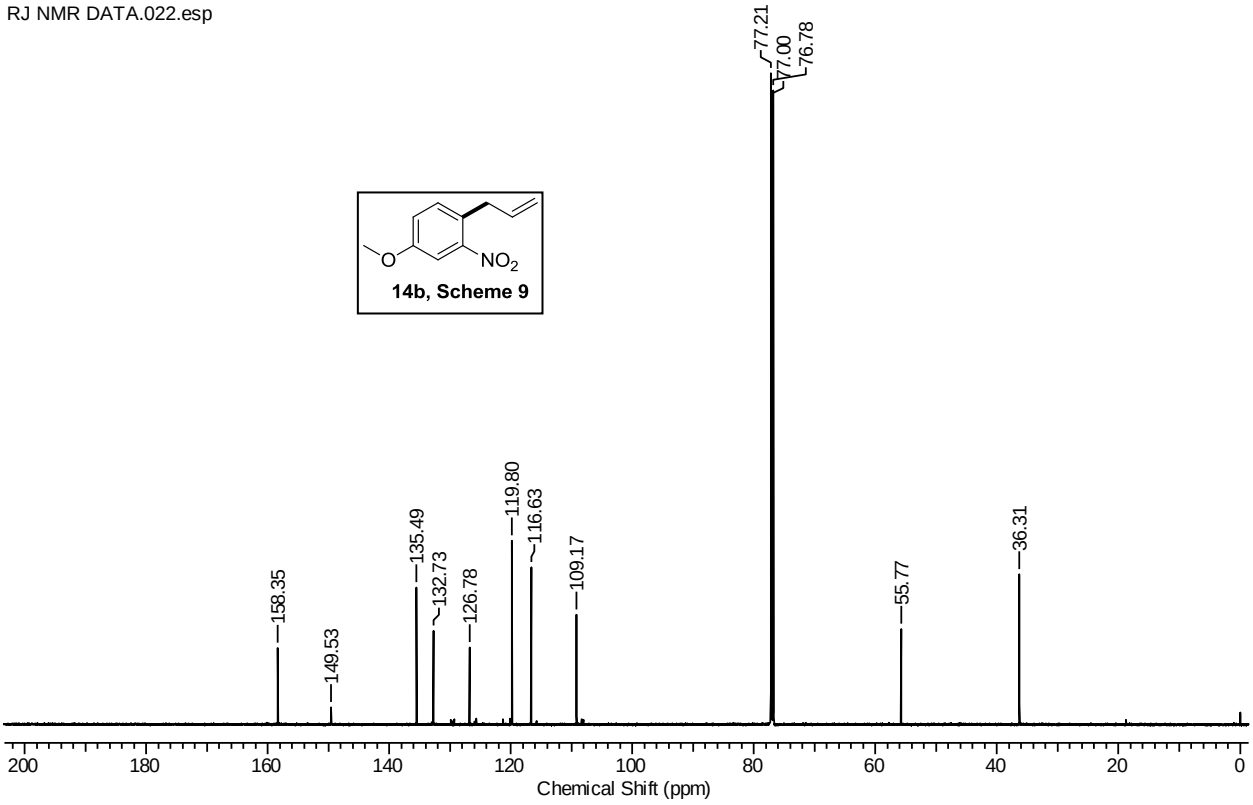

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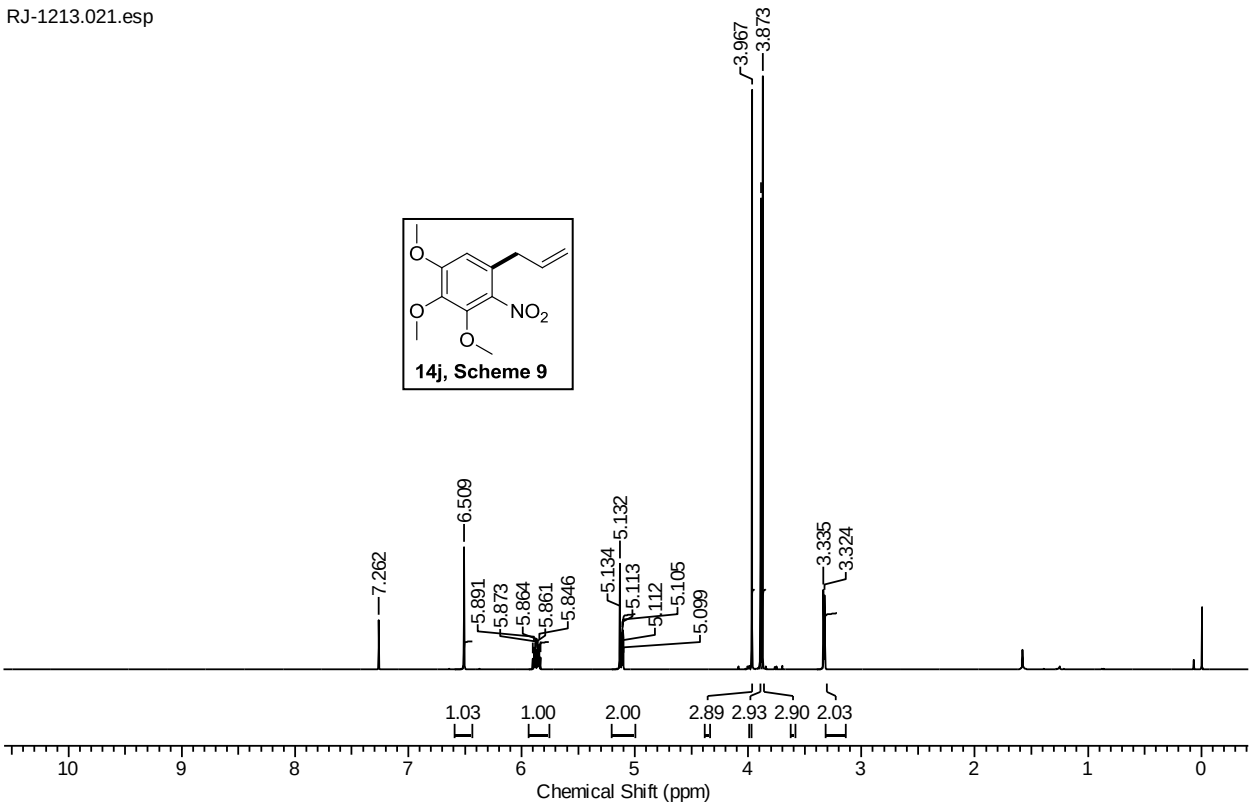


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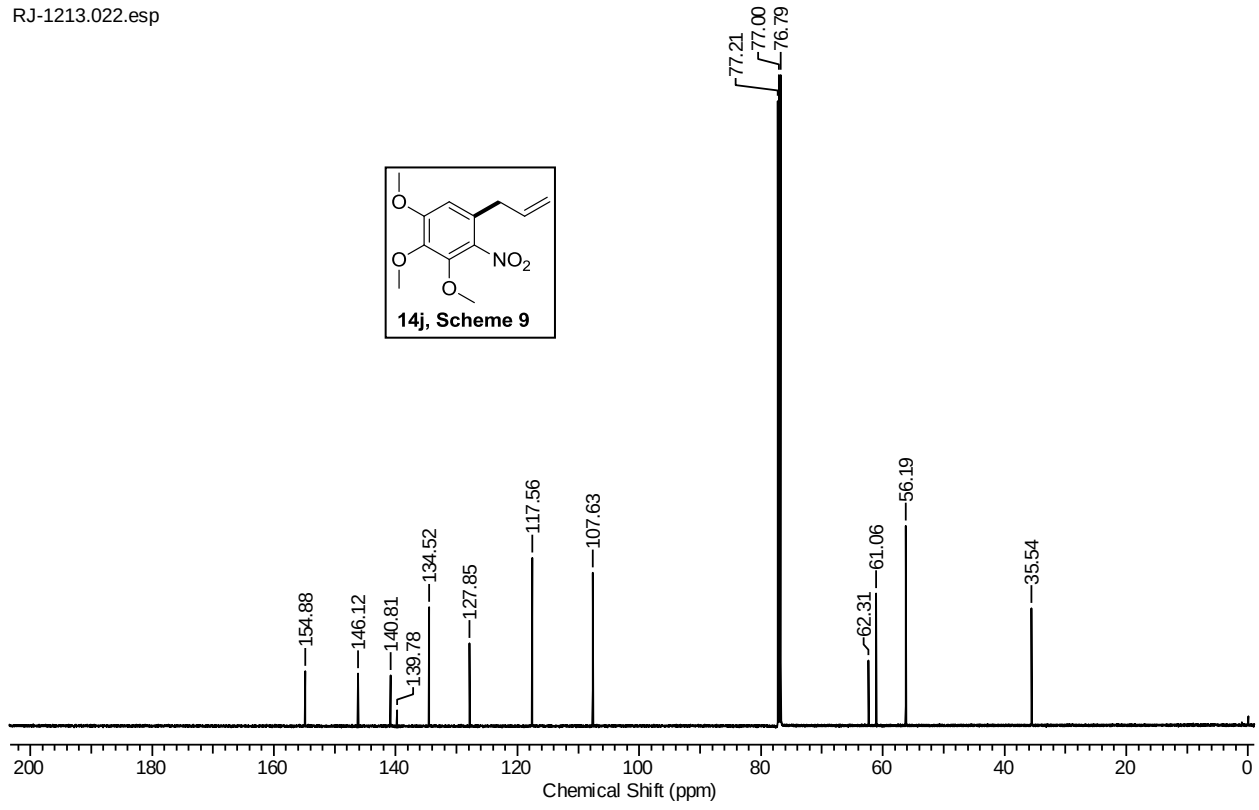

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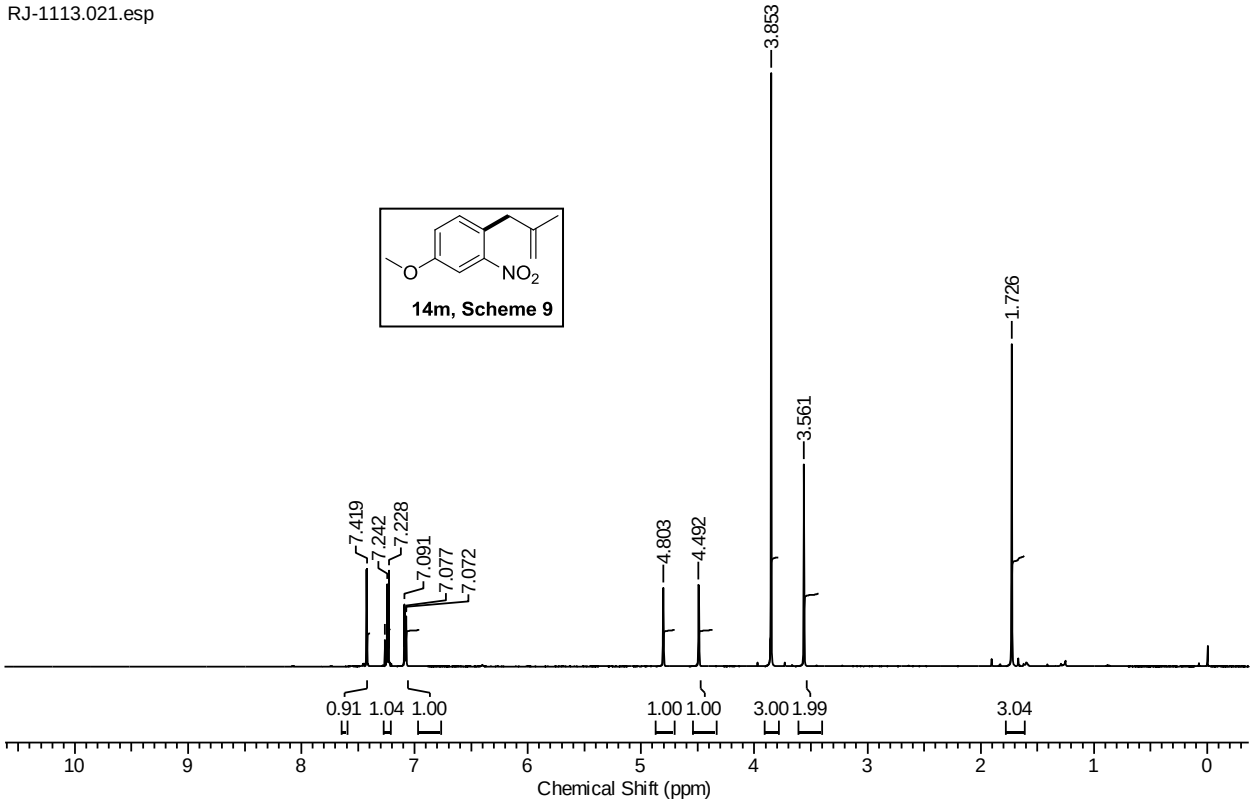


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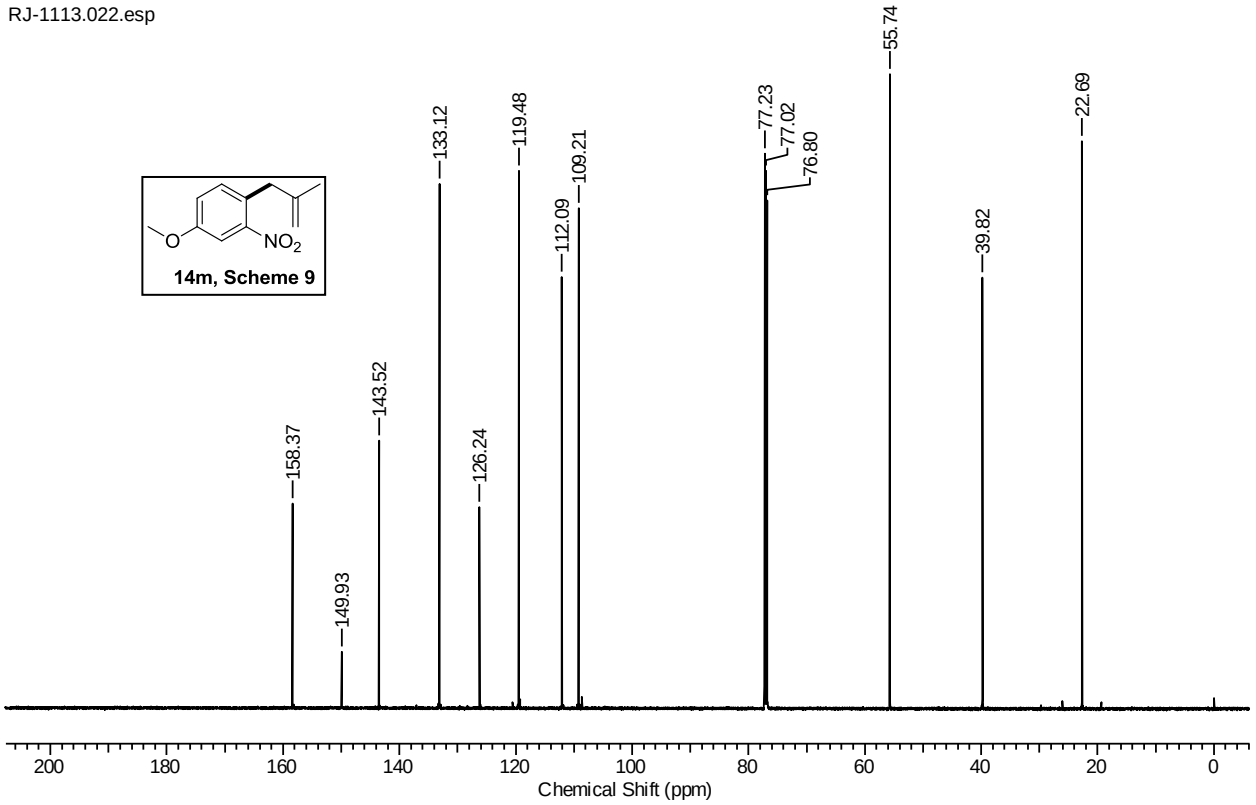

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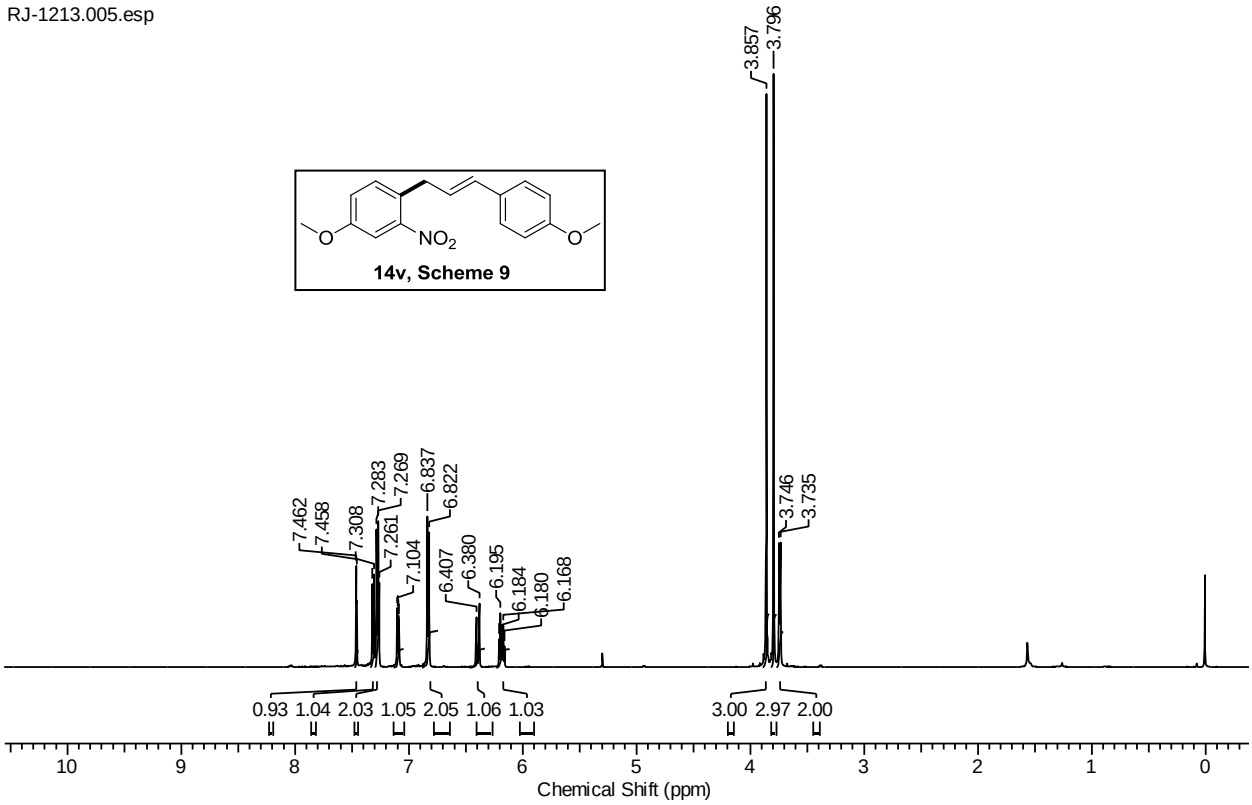


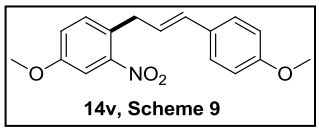


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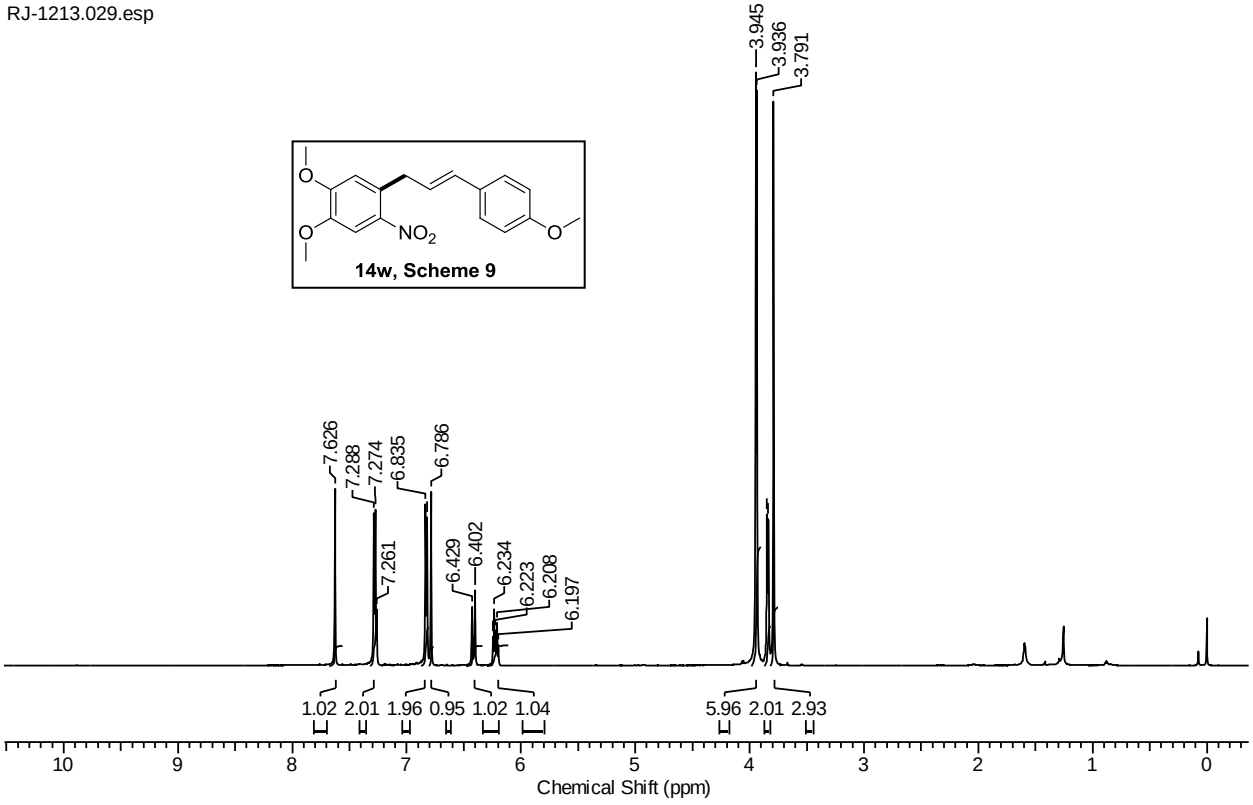


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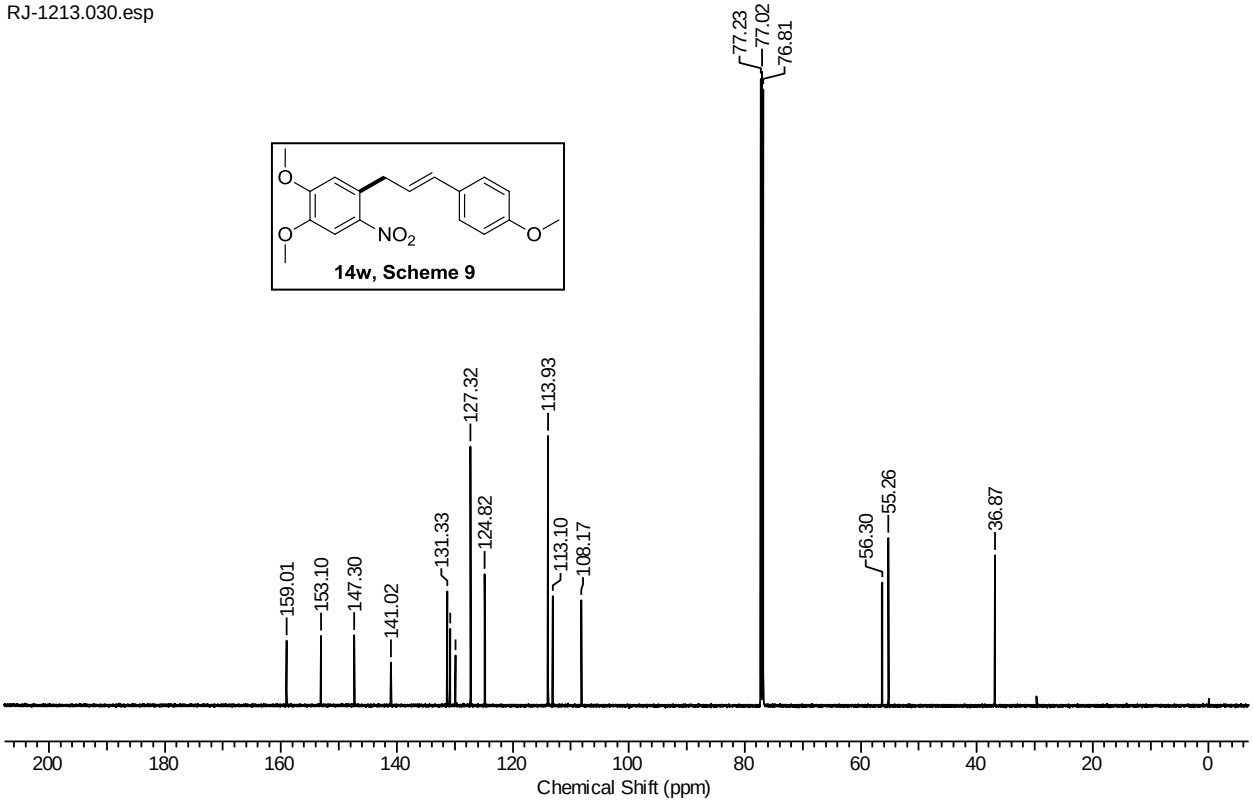

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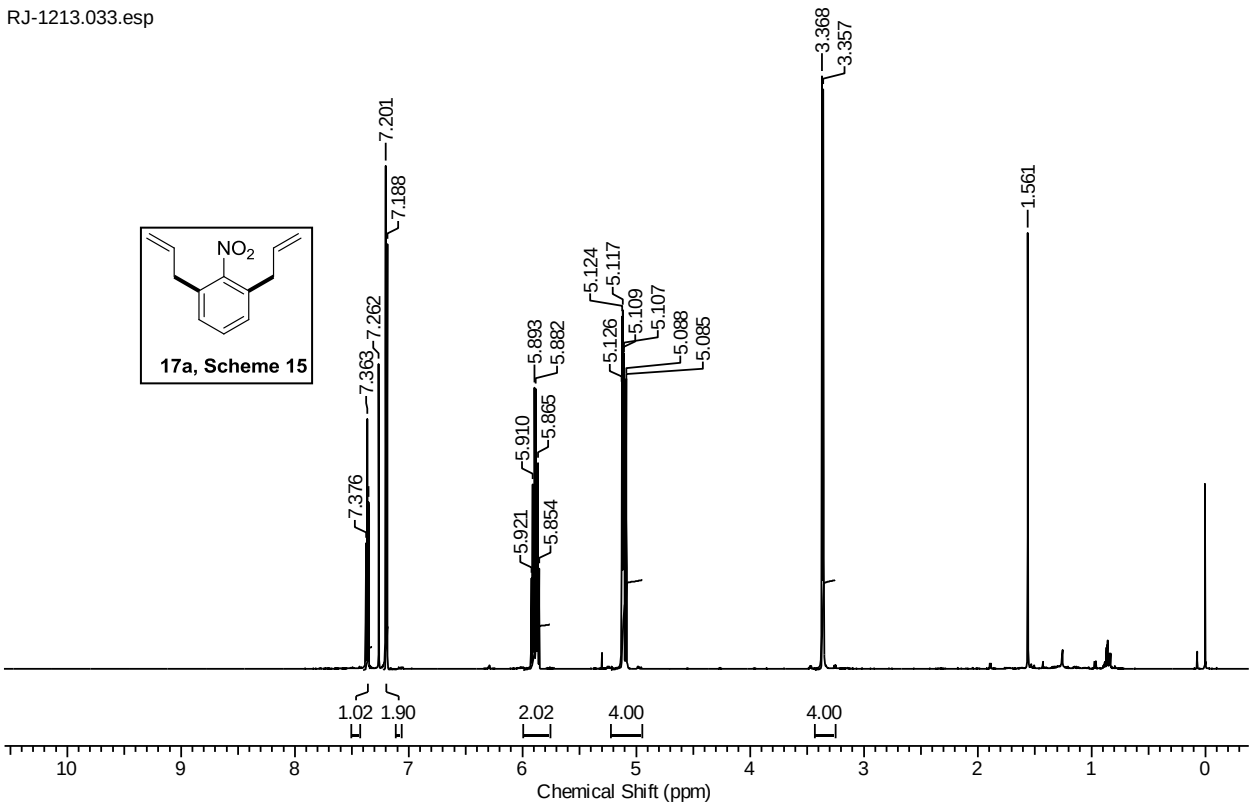


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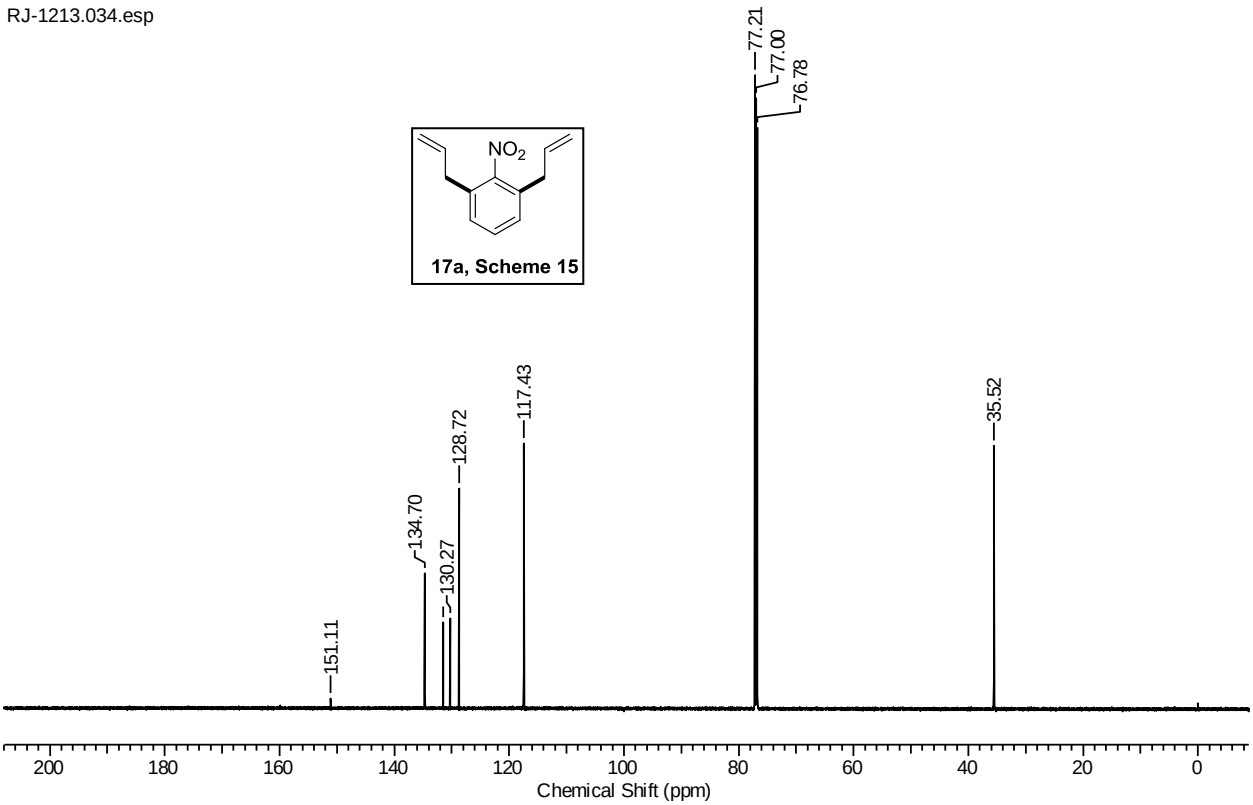

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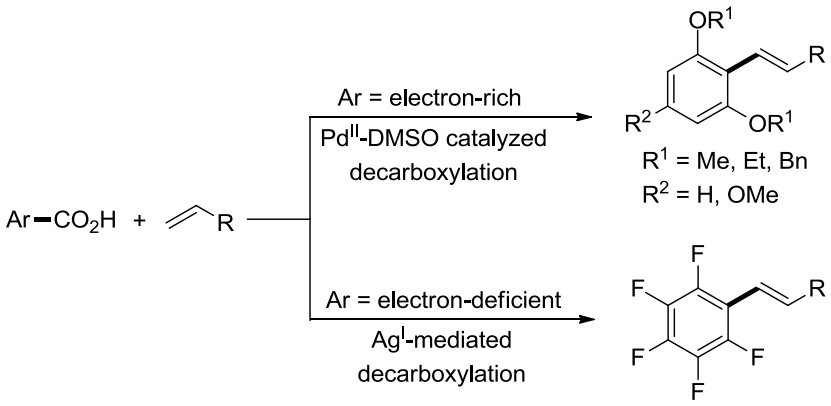
# CHAPTER III

## Substrate-Dependent Mechanistic Divergence in Decarboxylative Heck Reaction at Room Temperature



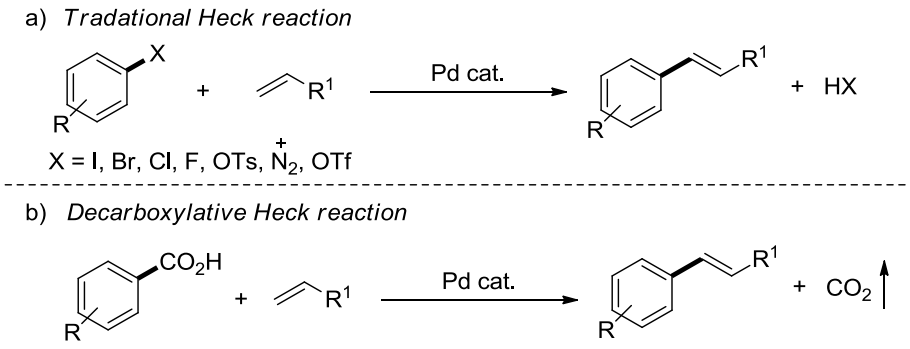

***Abstract:*** We report herein, a Pd(II)-catalyzed Heck-type coupling between arene carboxylic acids and alkenes at room temperature. Mechanistically, the reaction proceeds in two distinct pathways where electron-rich substrates undergo a palladium(II)-catalyzed decarboxylation and electron-deficient substrates proceed through silver(I)-assisted decarboxylation. Dimethylsulfoxide (DMSO) or sulfide ligands have positive and negative roles in the reaction outcome respectively. The present protocol is combined for the peptide modification under physiological conditions.

1. Hossian, A.; Bhunia, S. K.; Jana, R. *J. Org. Chem*. **2016**, *81*, 2521-2533.

# Substrate-Dependent Mechanistic Divergence in Decarboxylative Heck Reaction at Room Temperature

## III. 1. Introduction

The Heck reaction is one of the most attractive tools for the construction of C-C bonds between olefins and arenes.[1] It is widely used in small molecule synthesis, natural product synthesis, polymers, material science and also in bioorganic chemistry in both the laboratory and industrial scale (Figure 1).[2] Mizoroki[1g] and Heck[1f] first independently developed the palladium-catalyzed arylation of an alkene with an aryl electrophiles, today known as the classic Mizoroki-Heck reaction. Over the past decades, a variety of aryl halides,[3] aryl triflates,[4] aryl diazonium salts,[5] aryl phosphates,[6] and also arylsulfonyl halides,[7] have been used as an aryl electrophiles in the Mizoroki-Heck reactions. Significant advances for the development of new catalytic methods and mechanistic insight have also been well-studied in the traditional Heck reactions.[8] But still several drawbacks are there in the clasical Mizoroki-Heck reactions. From the environmental standpoint, the reaction producces stoichiometric amount of halide waste from the corresponding aryl halides and availability of the halogenated arene substrates is also limited and expensive. Moreover, some of the organometallic species are unstable, air and moisture sensitive thus limits their practical applicability. Alternatively, arenes carboxylates are low-cost, commercially available, air and moisture stable have been successfully accomplished in the Heck type reactions introducing a novel decarboxylative cross-coupling strategy (Scheme 1).




**Scheme 1.** Mizoroki-Heck reaction

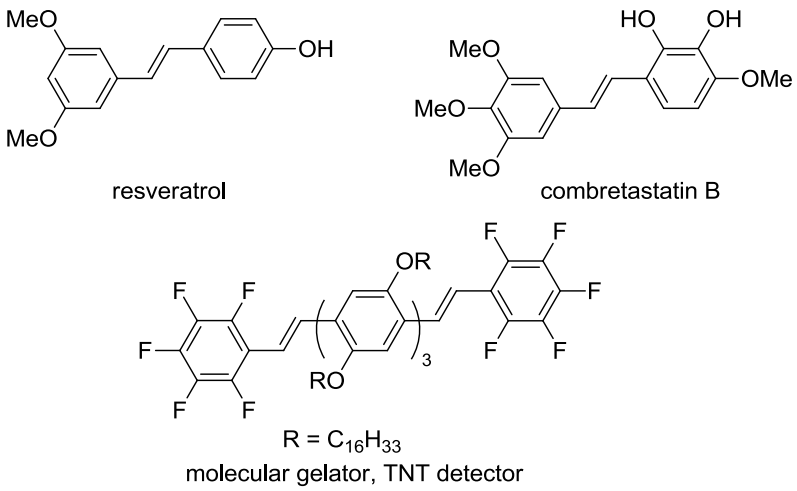
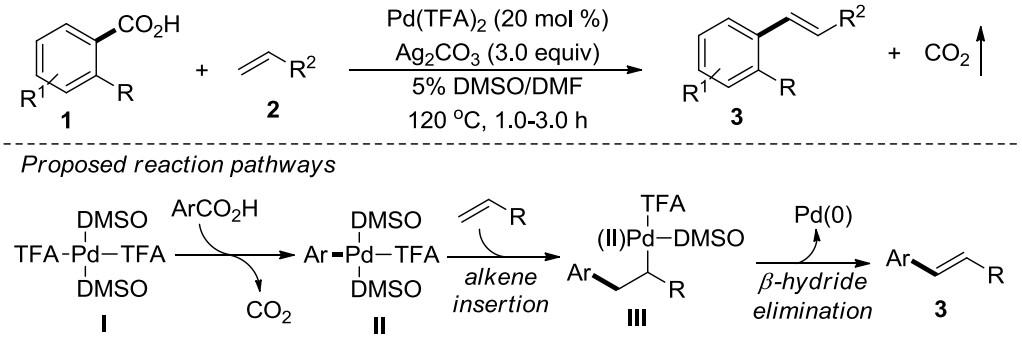



**Figure 1.** Representative example of some important stilbenes

## III. 2. Review

In a seminal report in 2002, Myers and coworkers disclosed an efficient method for palladium-catalyzed decarboxylative Heck-type olefination of arenecarboxylic acids with styrene and *α*,*β*-unsaturated carbonyl compounds (Scheme 2).[9] In the reaction, they used a catalytic amount of $Pd(TFA)_2$ in 5% DMSO-DMF solvent and a stoichiometric amount of $Ag_2CO_3$ as a base as well as an oxidant for catalytic turnover. Based on NMR studies and X-ray crystallographic analysis,[10] they have proposed the reaction pathways, initially carboxyl exchange between palladium(II) bis(trifluoroacetate) and an arene carboxylate substrates, then rate-determining palladium mediated decarboxylation to genertaes an arylpalladium(II) trifluoroacetate intermediate **II** where two DMSO molecules were bound to the intermediate in trans fashion through S-binding site. Here DMSO acts as a ligands on palladium and renders stability to the intermediates. Then the arylpalladium(II) trifluoroacetate intermediate undergoes migratory alkene insertion and finally *β*-hydride elimination afforded the desired olefin product. From the study they have observed that the reactivity differences between arylpalladium(II) species generated by decarboxylative palladation and the same phosphine ligated palladium(II) intermediate produced in conventional Heck reactions. Specifically, they have found that more electron-rich alkenes react preferentially with an arylpalladium(II) trifluoroacetate intermediate generates by decarboxylative palladation, whereas an opposite trend was

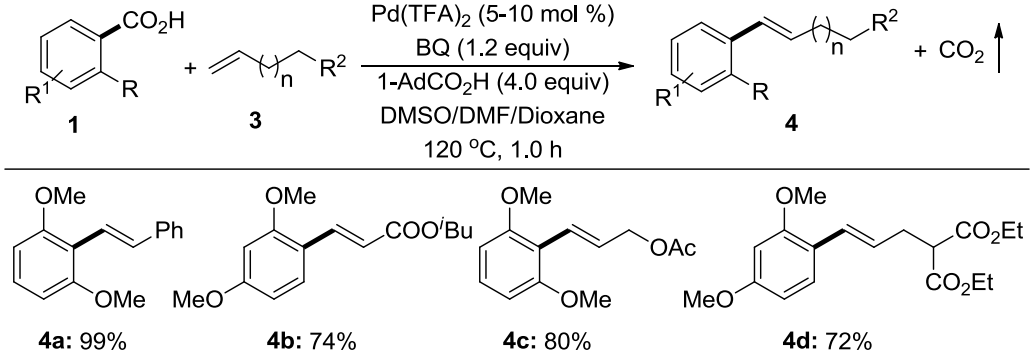
found in conventional Heck reactions. In addition, they have found that the aralkylpalladium(II) trifluoroacetate intermediate which is formed upon olefin insertion is stable as compared to the corresponding phosphineligated aralkylpalladium(II) complexes in traditional Heck reactions. They have also crystallographically characterized an aralkylpalladium(II) trifluoroacetate intermediate derived from arylpalladium(II) insertion into norbornene and in the structure they have observed that still one S-bound dimethyl sulfoxide ligand and one trifluoroacetate group is bound with the palladium in the distorted square-planar palladium(II) intermediate and subsequent *β*-hydride elimination afforded the desired product. The Myers's experimental results in decarboxylative Heck reaction was further cross validated by the Liu group through theoritical calculations.[11]




**Scheme 2.** Palladium-catalyzed decarboxylative Heck reaction

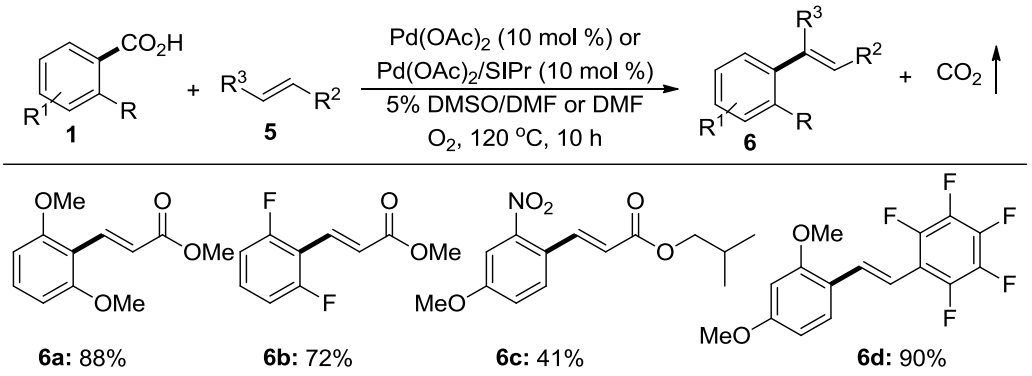
Although, the Myers work represents a breakthrough development for the palladium catalyzed decarboxylative cross-coupling reactions, still several limitations there were for practical application such as higher catalyst loading, requirement of super stoichiometric toxic silver salt and high reaction temperature. Also, they have showed limited scope with respect to olefinic substrates in the reaction. In this vein, the Su group have developed an efficient methodology for the decarboxylative Heck coupling of arenecarboxylic acids with a wide range of alkene substrates including unactivated terminal alkenes (Scheme 3).[12] In the reaction, they have employed 1-adamantanecarboxylic acid as an additive and inexpensive 1,4-benzoquinone (BQ) as an oxidant on palladium for catalytic tournover which is alternative to stoichimetric toxic

silver carbonate in the Myers method. However, the major limitation of the Su method is that only highly electron rich arene carboxylic acids underwent the reaction.

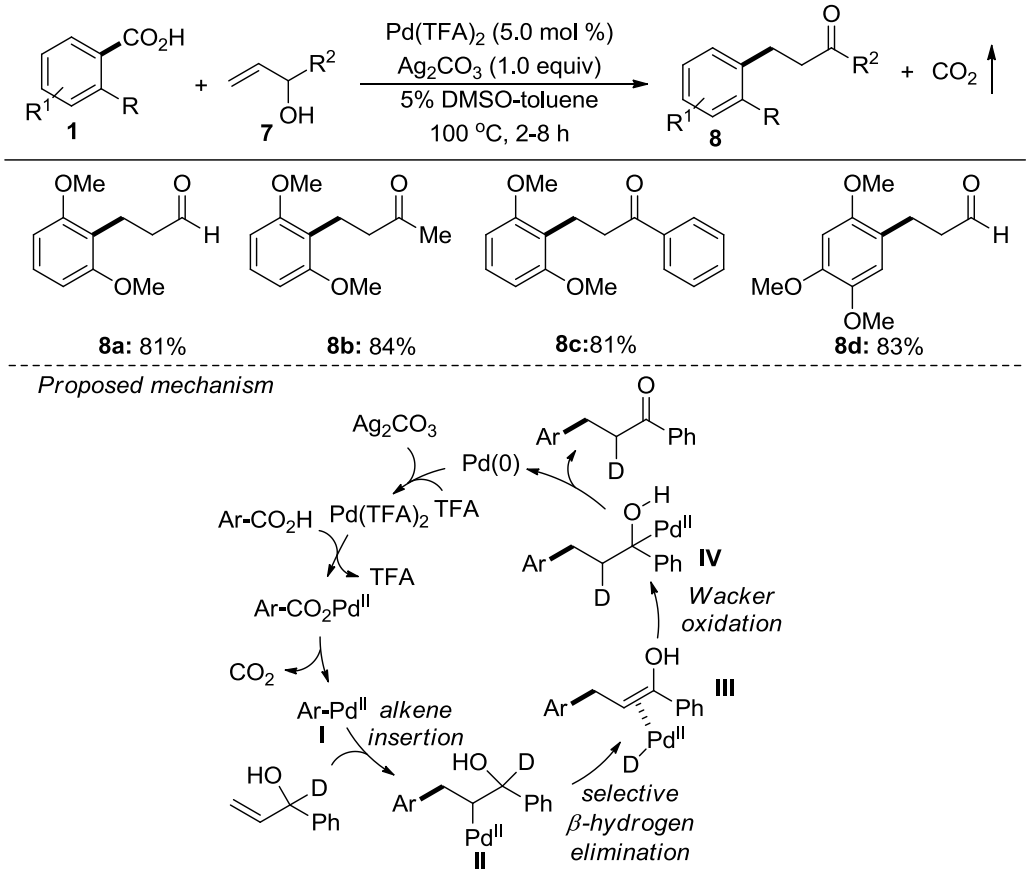



**Scheme 3.** Palladium-catalyzed decarboxylative Heck coupling with simple alkenes

In 2010, the Su group has developed a new Pd-catalytic system for the decarboxylative Heck coupling of various arene carboxylic acids with a wide range of olefins by using dioxygen as an oxidant for catalytic cycle (Scheme 4).[13] They found that for electron-rich aromatic carboxylic acids only $Pd(OAc)_2$ catalyst is sufficient for this transformation under oxygen atmosphere. But electron-deficient benzoic acids afforded low yield of the desired product under the similar conditions. This is presumably due to the poor reactivity of the Pd(II) catalyst toward decarboxylation of electron-deficient benzoic acids. The previous studies by Goossen, Larrosa, and Su, they have established that silver salts is effective for the decarboxylation of electron-deficient benzoic acids.[14] The difference in the reactivity between Ag(I) and Pd(II) towards decarboxylation of aromatic carboxylic acids may be due the fact that Ag(I) is more electron-rich than Pd(II) and Ag(I) is responsible for the decarboxylation of electron deficient benzoic acids. Therefore, they have used electron-donating ligand such as *N*-heterocyclic carbene on palladium catalyst and interestingly the yield of the reaction was improved. Finally, they have found $Pd(OAc)_2$/SIPr (SIPr = 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene) catalytic combination is effective for this transformation for electron deficient arene carboxylic acids under dioxygen pressure providing moderate to good yields (Scheme 4).




**Scheme 4.** Decarboxylative Heck coupling with dioxygen as the terminal oxidant

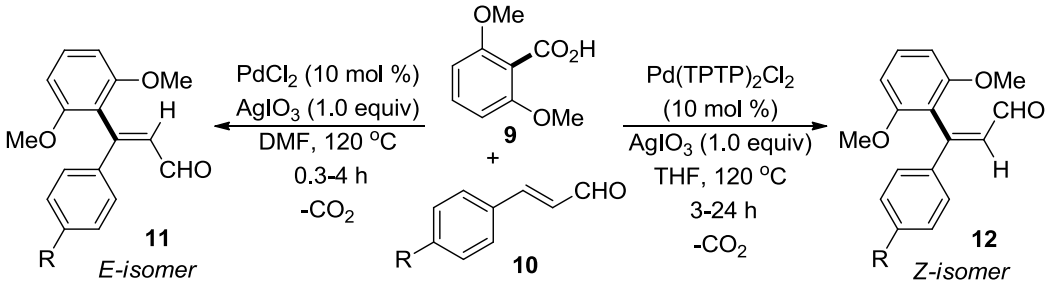



**Scheme 5.** Selective *β*-hydride elimination in the decarboxylative Heck coupling

In 2013, another interesting example of oxidative decarboxylative Heck type reaction was reported by the Jiang group.[15] They have developed a simple and efficient protocol for the palladium-catalyzed decarboxylative Heck type reaction of arene carboxylic acids with wide range of allylic alcohols to make *β*-aryl ketones and aldehydes

through selective *β*-hydrogen elimination (Scheme 5). To understand the reaction mechanism, they have performed several control experiments and proposed the reaction mechanism in scheme 5. First aryl-palladium intermediate **I** is generated through the palladium-mediated decarboxylation. Then the aryl-palladium intermediate **I** undergoes insertion reaction into the allylic alcohol to produce intermediate **II** and through the selective *β*-H elimination generated intermediate **III** from the intermediate **II**. The critical intermediate **IV** is formed via Pd-H insertion similar to the oxidative Wacker process. Finally, the desired products is obtained through *β*-H elimination of R-OH group or the anion-assisted reductive elimination from the intermediate **IV** and regenerated the palladium(II) active catalyst via the oxidation of $Ag_2CO_3$.

Very recently, another very interesting example of decarboxylative Heck-type reaction was reported by the Li group (Scheme 6).[16] They have developed a system for controlling the *Z*/*E* selectivity in the palladium catalyzed decarboxylative Heck type arylation reaction of *trans*-cinnamaldehydes by switching the reaction solvent. They found exclusive *Z*-isomer formation in good yield and stereoselectivity in THF, whereas the reaction afforded kinetically control *E*-isomer in DMF. Based on experimental and theoretical study they have explained the *Z*/*E* selectivity switch in the reaction. When DMF solvent was used in the reaction, the reaction proceed through the standard Heck type addition-elimination process providing the *E*-isomer. Whereas in THF solvent the reaction proceed via tautomerization of Pd(II)enolate and leads to the formation of thermodynamically more stable *Z*-isomer.

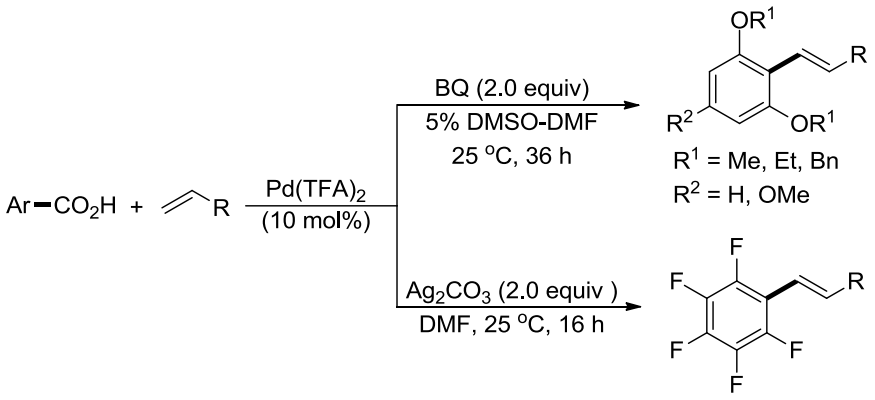



**Scheme 6**. *Z*/*E* selectivity in the palladium-catalyzed decarboxylative Heck type reaction

## III. 3. Present work

The decarboxylative cross-coupling of arene carboxylic acids with olefins provides an attractive approach for the alkene functionalization.[17] However, one of the major pitfalls in the decarboxylative cross-coupling is the requirement of high reaction temperature (120-190 $^{o}$C) which restricts its application in the synthesis of complex molecular frameworks. Owing to the prevalence of stilbenes in numerous natural product, bioactive molecules and high tech materials,[18] we were particularly interested to the development of decarboxylative Heck-type coupling at room temperature.

Although, palladium-catalyzed decarboxylative coupling of nitroalkanes[19] and α-ketocarboxylic acids[20] at room temperature is known, there is no report of decarboxylative cross-coupling of arene carboxylates at room temperature. We report here for the first time a palladium-catalyzed decarboxylative Heck-type coupling at room temperature (Scheme 7). We also report the substrate-dependent mechanistic variation and distinct role of dimethylsulfoxide/sulfide ligands in the present transformation.




**Scheme 7.** Decarboxylative Heck-arylation with olefins at room temperature

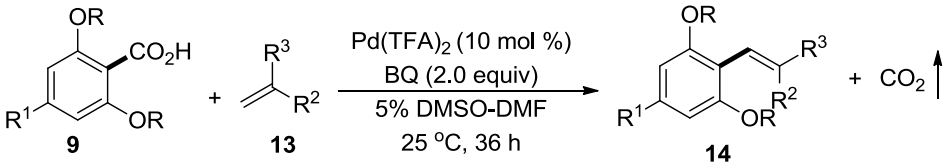
## III. 4. Results and discussion

From literature it was evident that *o*,*o*'-disubstitution facilitates carbon dioxide extrusion.[15,21] In addition, from our previous experience with the decarboxylative allylation of *ortho*- nitrobenzoic acids, we realized that the incipient anion which is generated after decarboxylation needs to be stabilized for further cross-couplings.[22] Thus

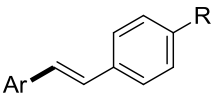
we rationalized that either 2,6- dimethoxy benzoic acid or pentafluorobenzoic acid could be model substrates to study room temperature decarboxylative cross-coupling which will be a major advancement in this field.

Initially, we started screening for decarboxylative Heck reaction between 2,6-dimethoxybenzoic acid and styrene under the Myers's original conditions. But a trace amount of corresponding Heck product was isolated at room temperature. However, a good yield of the coupling product was isolated after 36 h stirring. In search for alternative oxidants to stoichiometric silver carbonate, 1,4-benzoquinone (BQ) was found to be suitable.[12] Finally, an excellent yield of the stilbene product was obtained after stirring the reaction mixture for 36 hours at room temperature with 10 mol % palladium catalyst loading and 2.0 equiv of 1,4-benzoquinone.

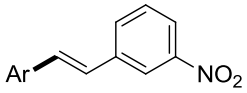
Being encouraged, several alkene partners were examined. A wide variety of styrenes having electron-withdrawing and electron-donating substituents underwent decarboxylative coupling providing high to excellent yields (Scheme 8). Fluoro-, chloro-, bromo-, (**14c-14e**, **14ae**, Scheme 8) and remarkably acetoxy- (**14g**, **14af**, Scheme 8) groups were intact under the reaction conditions demonstrating the mild nature of this present protocol. Besides styrenes, activated alkenes such as acrylonitrile, (**14n**, Scheme 8) acrylates (**14o-14r**, **14ag**, Scheme 8) also provided the corresponding cross-coupling products. Interestingly, unactivated allylbenzenes (**14s-14u**, Scheme 8), allyl acetate (**14v**, Scheme 8), allyl malonate (**14x**, **14ah**, Scheme 8), and unactivated terminal alkene (**14y**, Scheme 8) also afforded the corresponding coupling products in good to moderate yields and good styrenyl selective products under slightly higher catalyst loading. The Heck coupling with an allyl alcohol (**14w**, Scheme 8) provided the corresponding ketone product via selective $\beta$-hydride elimination in moderate yield.[6b] Remarkably, 1,4-divinylbenzene provided the double cross-coupling product in one stroke (**14m**, Scheme 8). 2,6-Diethoxy- (**14z**, Scheme 8) and 2,6-dibenzyloxy (**14aa**, Scheme 8) benzoic acid also provided the corresponding coupling products in excellent yields. However, benzoic acid, mesitylenecarboxylic acid, 2-methoxy benzoic acid, and heteroaryl carboxylic acids such as pyridine-2-carboxylic acid, and benzofuran-2-carboxylic acid did not furnish any desired product. It was found that *o*,*o*-dialkoxy substitution is essential for



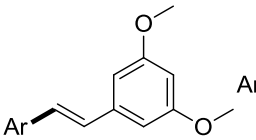

Ar = 2,6-dimethoxybenzene



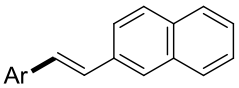

**14a**: R = H, 94%
**14b**: R = $^{t}$Bu, 94%
**14c**: R = F, 87%
**14d**: R = Cl, 82%
**14e**: R = Br, 74%
**14f**: R = OMe, 60%
**14g**: R = OAc, 95%



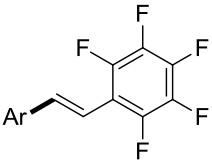

**14h**: 93%



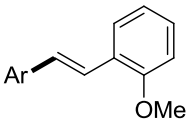

**14i**: 84%



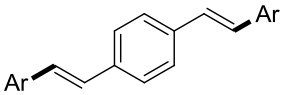

**14j**: 86%



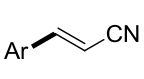

**14k**: 85%



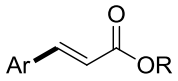

**14l**: 76%



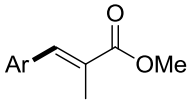

**14m**: 72%



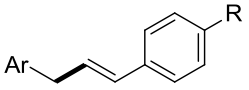

**14n**: 64%
(*E*/*Z* = 4:3)



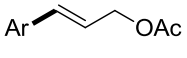

**14o**: R = Me, 81%
**14p**: R = $^{n}$Bu, 74%
**14q**: R = Ph, 73%



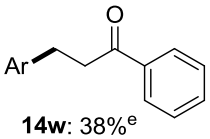

**14r**: 40%



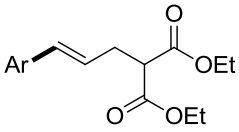

**14s**: R = H, 55%[d], (l/b = 50:1)
**14t**: R = F, 57%[d], (l/b = 49:1)
**14u**: R = OMe, 42%[d] (l/b = 49:1)



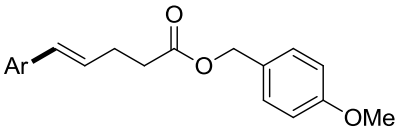

**14v**: 67 %[d], (l/b = 30:1)



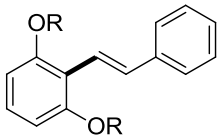

**14w**: 38%[e]




**14x**: 65%[d] (l/b = 25:1)

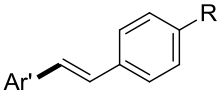



**14y**: 40%[d], (l/b = 20:1)

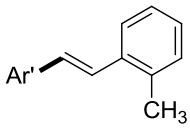



**14z**: R = Et, 90%
**14aa**: R = Bn, 75%

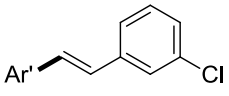
Ar' = 2,4,6-trimethoxybenzene



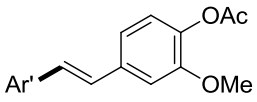

**14ab**: R = H, 93%
**14ac**: R = Ph, 82%



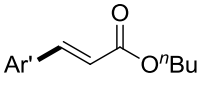

**14ad**: 90%



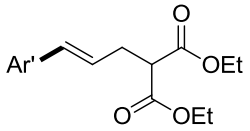

**14ae**: 91%




**14af**: 85%




**14ag**: 70%




**14ah**: 62%[d], (l/b = 12:1)

**Scheme 8.** Substrate scope with electron-rich carboxylic acids

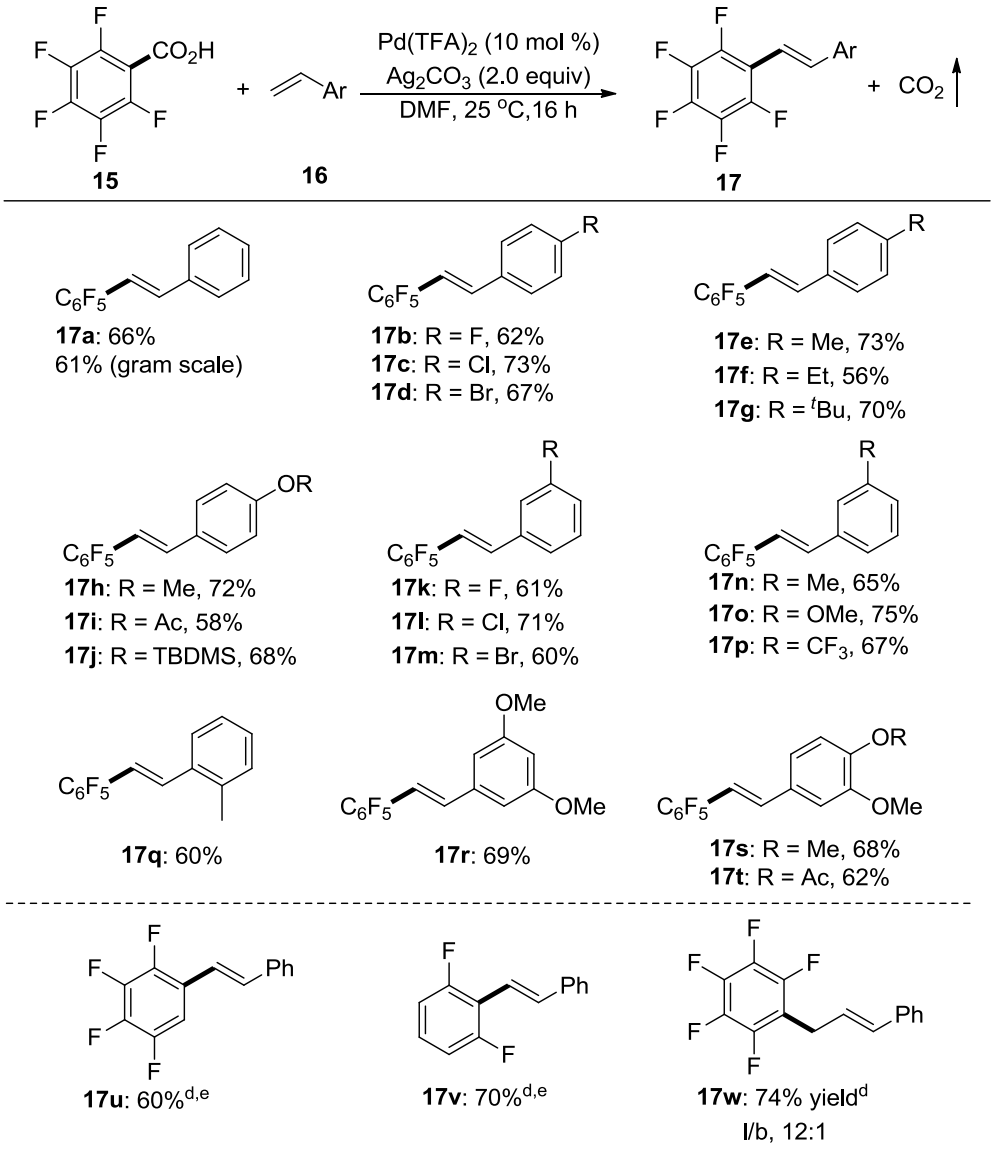
*Note*: [a]The reaction was carried out in 0.2 mmol scale, 0.06 M. [b]Yield refer to here is the average of at least two experiments. [c]Unless otherwise stated *E/Z* ratio of the Heck products are >20:1 as determined by $^1$H NMR. [d]20 mol % $Pd(TFA)_2$ and 3.0 equiv BQ were used. [e]Reaction time 48 h.

decarboxylative coupling at room temperature presumably due to coordination between oxygen and aryl-palladium species.

Next we turned our attention to the pentafluoroarenes as they exhibit distinct chemical and physical properties to their hydrocarbon counterpart.[23] Also an increasing use of perfluorinated compounds in material science, biomedical and bioanalytical research, defense, refrigeration, and domestic appliances has been observed.[24] Therefore, introduction of perfluorinated moiety into the organic backbone has become a fascinating field of research in the last years.[25] However, the metal-catalyzed cross-coupling reaction with this highly electron-deficient arenes poses a great challenge, due to poor coordination with the metal center and reluctance to undergo cross-coupling. A seminal work of palladium-catalyzed Heck coupling between pentafluorohalobenzene (X = I, Br) and styrenes was reported by the Espinet and Milstein groups.[26] Recently, an oxidative Heck coupling between pentafluorobenzene and styrenes were reported by the Zhang group,[27a] and a decarboxylative allylation of pentafluorobenzoates was reported by the Gooβen group at 120 $^o$C and 110 $^o$C respectively.[27b] Direct oxidative cross-coupling with perfluoroarenes also an emerging field of research.[28]

To examine decarboxylative Heck coupling with electron-deficient substrates, pentafluorobenzoic acid was employed under the optimized reaction conditions but no product was formed. Since $Pd^{II}/Ag^{I}$ combination is essential for the decarboxylative coupling of electron-deficient substrates,[29] benzoquinone was replaced by silver carbonate. Still no Heck product was isolated. Surprisingly, the reaction in pure DMF only provided the Heck product at room temperature. This is in sharp contrast to the earlier reports where addition of 5% dimethylsulphoxide (DMSO) in dimethylformamide (DMF) was found to improve the yield at elevated temperature. Finally, the desired

Heck-products were obtained with 10 mol % $Pd(tfa)_2$ and 2.0 equiv of $Ag_2CO_3$ in good yields after 16 h stirring at room temperature.




**Scheme 9.** Substrate scope with perfluorobenzoic acids

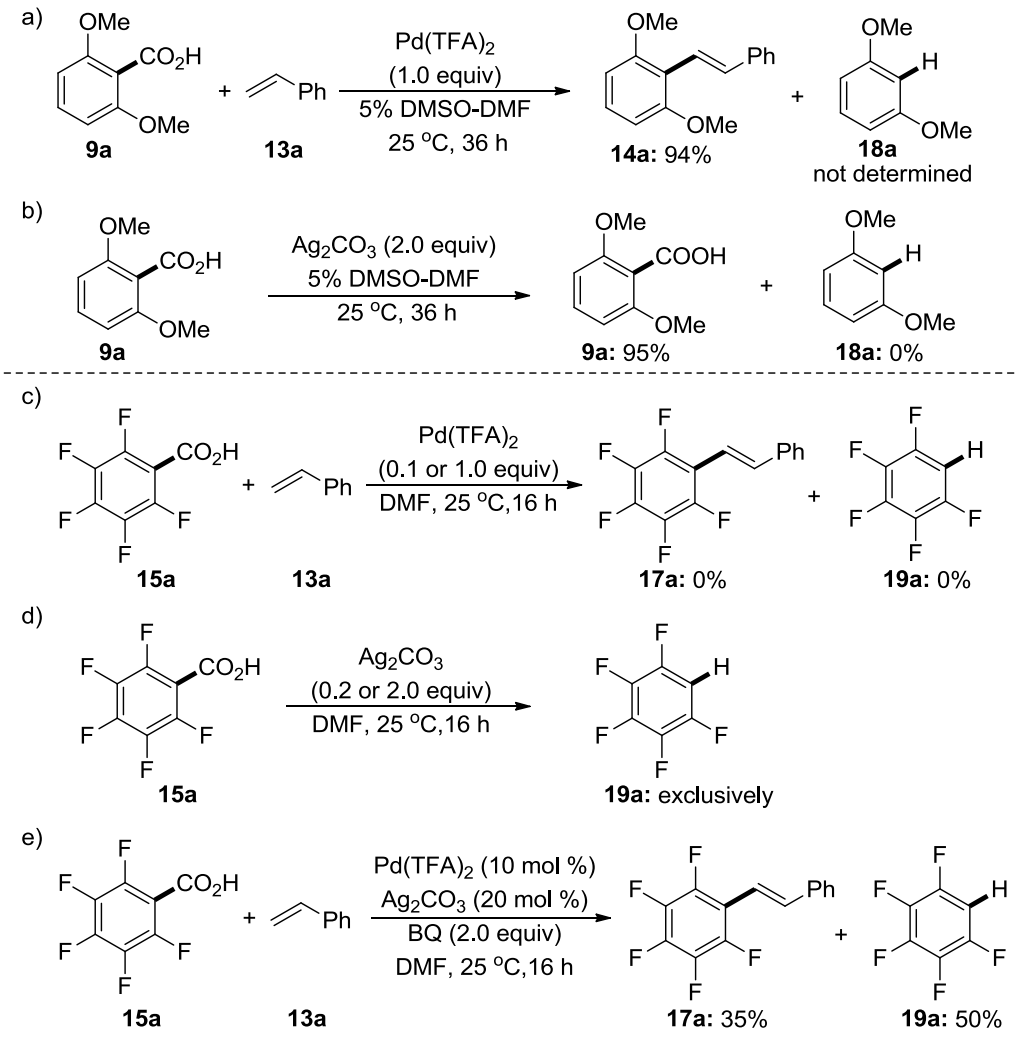
*Note*: [a]The reaction was carried out in 0.2 mmol scale, 0.06 M. [b]Yield refer to here is the average of at least two experiments. [c]*E/Z* ratio of the Heck products are >20:1 as determined by $^1H$ NMR. [d]120 °C was used. [e]20 mol % $Pd(TFA)_2$, 3.0 equiv $Ag_2CO_3$ and 5% DMSO-DMF were used, reaction time 4 h.

With this optimized reaction conditions we explored the substrate scope. A wide variety of substituted styrenes provided the Heck product in high yields. Besides alkyl substituents, halogens (**17b-17d**, **17k-17m**, Scheme 9), labile acetoxy (**17i**, **17t**, Scheme 9) and *tert*-butyldimethylsilyoxy (**17j**, Scheme 9) groups were compatible under these mild reaction conditions. The reaction was also reproduced in gram scale in comparable yield. However, 2,3,4,5-tetrafluoro and 2,6-difluoro benzoic acids provided the coupling product at 120 $^{o}$C (**17u**, **17v**, Scheme 9). Interestingly, the reaction with allylbenzene at 120 $^{o}$C provided the corresponding allylation product in high yield and selectivity (**17w**, Scheme 9). Activated alkenes such as methyl acrylate afforded only a trace amount of Heck product under the same reaction conditions.

## III. 5. Reaction mechanism

In their report, the Myers group applied a general reaction conditions for electron-rich and electron-deficient carboxylic acids. In addition, experimental and theoretical mechanistic investigation was performed exclusively based on the electron-rich substrates.[10,11] In their study with catalytic and stoichiometric palladium(II)trifluoroacetate, it was observed that decarboxylation occurs by palladium salt where silver salt acts as an oxidant for catalytic turnover.[16b] However, the mechanism for electron-deficient substrate was illusive. In this present study, we have also observed that electron-rich 2,6-dimethoxybenzoic acid undergoes decarboxylative Heck reaction by a catalytic amount of palladium(II) bistrifluoroacetate where silver(I) carbonate was replaced by benzoquinone for practical applications. A stoichiometric palladium salt also reproduced the same result in the absence of benzoquinone (Scheme 10a). Additionally, a control experiment suggests that even a super stoichiometric amount of silver(I) carbonate (2.0 equiv) did not furnish decarboxylation of the 2,6-dimethoxybenzoic acid in the absence of palladium at room temperature (Scheme 10b). However, exclusive decarboxylative protonation product was observed by the Larrosa group with 10 mol % Silver(I) carbonate at 120 $^{o}$C.[30] In sharp contrast, in the absence of silver salt the reaction with electron-deficient pentafluorobenzoic acid did not proceed even with stoichiometric amount of palladium(II) bistrifluoroacetate (Scheme 10c). However, either stoichiometric (2.0 equiv) or a catalytic amount (20 mol %) of silver(I) carbonate resulted in

decarboxylative protonation product exclusively (Scheme 10d). Additionally, a catalytic amount of silver(I) carbonate (20 mol %), palladium(II) bistrifluoroacetate (10 mol %), and benzoquinone (2.0 equiv) afforded the corresponding Heck product from the pentafluorobenzoic acid and styrene albeit in low yield (35%) (Scheme 10e). Therefore, electron-deficient substrates may follow a distinct pathway for the decarboxylative Heck reaction from electron-rich substrates at room temperature. A similar observation was also observed by the Su group where 2,4-dimethoxybenzoic acid underwent decarboxylative protonation with stoichiometric palladium(II)trifluoroacetate at 80 $^{o}$C but 2-nitrobenzoic acid was unreactive. On the other hand, electron-deficient 2-nitrobenzoic acid afforded decarboxylative protonation exclusively with super stoichiometric amount




**Scheme 10.** Control experiments

of silver(I) carbonate (3.0 equiv) only. Ultimately, a Pd/Ag bimetallic system was applied for the C-3 selective arylation of indoles with electron-deficient nitrobenzoic acids.[29,31]

Interestingly, in the earlier reports dimethylsulfoxide (DMSO) or other sulfide ligands exhibited a prominent role in decarboxylative, direct alkenylation or allylic C-H activations where addition of 5% DMSO as a cosolvent was found to improve yields and catalytic efficiency.[9,10,11,32] From NMR and crystal structure studies, the Myers group has also shown that DMSO acts as a ligand on the aryl-palladium species in decarboxylative Heck-type coupling.[10] In sharp contrast, for the first time we have observed that DMSO or sulfide ligand exhibit a negative role in the decarboxylative alkenylation reaction between pentafluorobenzoic acid and styrene at room temperature. A careful study revealed that the yield of the alkenylation product was decreased successively with the increase of DMSO (Figure 2) with respect to the pentafluorobenzoic acid. In lieu of pure DMF (Scheme 10d), 5% DMSO-DMF also furnished the decarboxylative protonation product exclusively suggesting that DMSO has no role in siver-mediated decarboxylation. Therefore, DMSO may act as a ligand on the palladium and influence negatively for the subsequent cross-coupling processes with electron-deficient carboxylic acids. The same trend was also observed with phenyl methyl sulfide. Although, the exact reason for this negative effect of DMSO is not clear at this moment but this room temperature decarboxylation will leads to the development of new cross-coupling

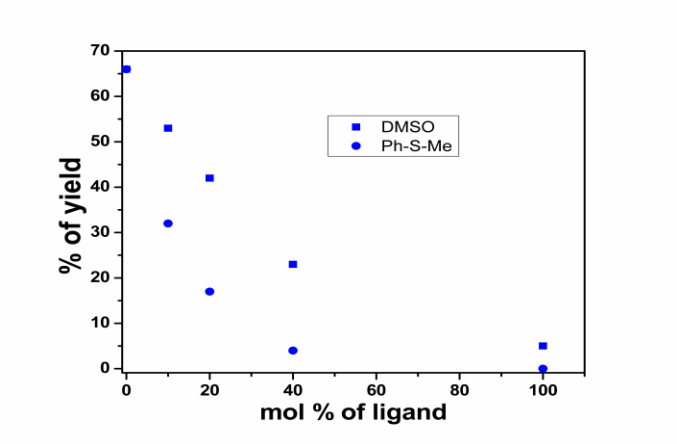
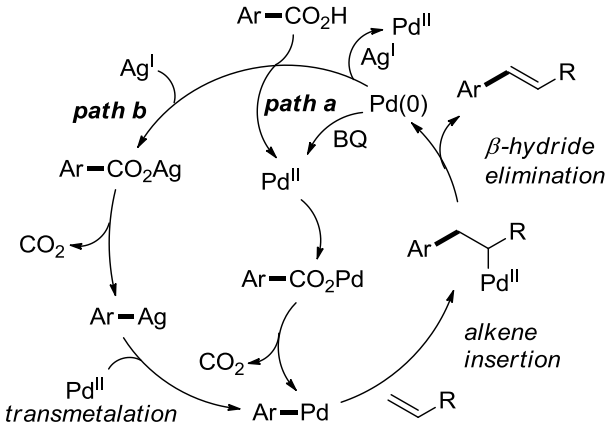



**Figure 2.** Negative role of sulfoxide or sulfide ligand in the heck reaction between pentafluorobenzoic acid and styrene at room temperature

reactions under mild conditions.

Based on earlier reports and the present study it is speculated that depending of the electronic nature of the carboxylic acids a mechanistic divergence is observed in the decarboxylative Heck coupling reaction. The electron-rich substrates may follow a palladium-catalyzed decarboxylation where dimethylsulfoxide acts as a ligand and benzoquinone plays as an oxidant for catalytic turnover as shown in ***path a***, Scheme 11.[27] Whereas, pentafluorobenzoic acid may undergo a silver-assisted decarboxylation which forms a aryl-palladium species after transmetalation as depicted in ***path b***, Scheme 11. Subsequently, the aryl-palladium species undergoes migratory alkene insertion and *β*-hydride elimination to provide the Heck product and palladium(0). Finally, the palladium(0) is oxidized either by silver(I) salt or benzoquinone in ***path a*** and ***path b*** respectively to complete the catalytic cycle.

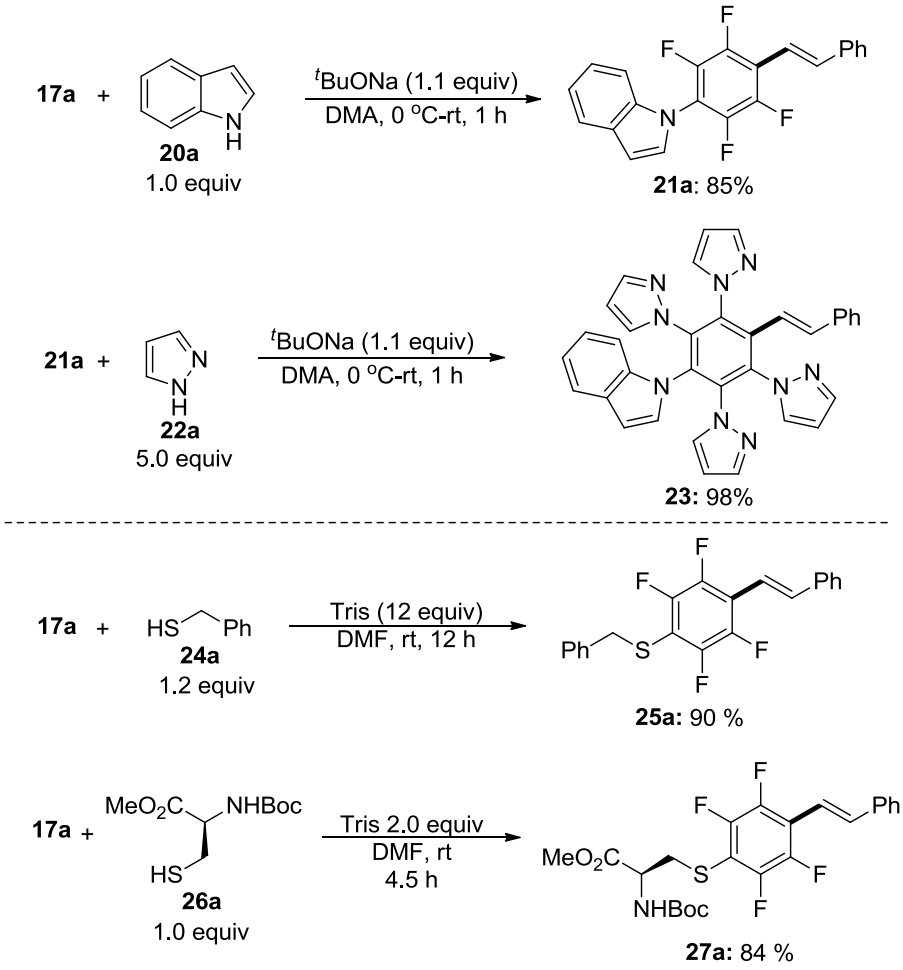



**Scheme 11.** Plausible mechanism

## III. 6. Product derivatization

Next we turned our attention to utilize the decarboxylative Heck product for further useful transformations. Under basic conditions, the pentafluoroarene moiety, **17a** undergoes an activated aromatic nucleophilic substitution ($S_NAr$) with indole selectively at the *para*-position to afford (**21a**, Scheme 12). The remaining fluorenes are further substituted by excess pyrazoles to provide (**23a**, Scheme 12).[33] Development of novel synthetic methods for the postsynthetic modification of peptide is an attractive research

field.[34] In this vein, we have applied the decarboxylative Heck product for the arylation with cysteine. To demonstrate with the sulfur nucleophiles, the Heck product **17a** was reacted with benzyl mercaptan to afford (**25a**, Scheme 12) in excellent yield. Similarly, it also underwent activated aromatic nucleophilic substitution ($S_NAr$) with the protected cysteine selectively at the *para*-position to provide (**27a**, Scheme 12).




**Scheme 12.** Product derivatization

## III. 7. Conclusion

In conclusion, we have developed a decarboxylative Heck-type coupling between arene carboxylic acids and alkenes at room temperature. A substrate-dependent mechanistic divergence was observed where electron-rich arene carboxylic acids undergo palladium-catalyzed decarboxylation and electron-deficient arene carboxylic acids undergo silver-assisted decarboxylation. Similarly, dimethylsulfoxide or other sulfide ligands exhibit

positive and negative roles respectively in the present transformation. The pentafluoroarene moiety obtained from the cross-coupling was further derivatized via activated aromatic nucleophilic substitution (SNAr) with nitrogen and sulfur nucleophiles. Therefore, this room temperature reaction sequence is useful for peptide modification under mild reaction conditions.

## III.8. Experiment section

**General experimental procedure for the decarboxylative Heck reaction between electron-rich carboxylic acids and alkenes**

To an oven-dried 15 mL sealed tube, a mixture of carboxylic acids (0.20 mmol, 1.0 equiv), palladium (II)trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv) and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv) was taken. Then dry DMF (3.0 mL) and DMSO (0.15 mL) were added to it. After purging the reaction vessel with nitrogen, the corresponding alkene (0.30 mmol, 1.5 equiv) was added to the reaction mixture via microliter syringe and the vessel was sealed with a screw cap. The reaction mixture was allowed to stir for 36 h at room temperature. After completion (as detected by TLC), the reaction mixture was poured into water (20 mL) and extracted with ethyl acetate (30 mL). The organic layer was washed with aqueous NaOH solution (2N, 10 mL), water (10 mL), and brine solution (10 mL), dried over anhydrous $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography using ethyl acetate/hexane as eluent to afford the desired product.

**1-(2,6-Dimethoxystyryl)benzene, 14a, Scheme 8**.[35] The same general procedure was followed by using 2,6-dimethoxybenzoic acid (36.5 mg, 0.2 mmol, 1.0 equiv), styrene (35 µL, 0.3 mmol, 1.5 equiv), palladium (II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 96:4 hexane/ethyl acetate) afforded the desired product as a colourless oil (45 mg, 94%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.61 (d, $J$ = 6.8 Hz, 1H), 7.57 (d, $J$ = 7.8 Hz, 2H), 7.49 (d, $J$ = 16.5 Hz, 1H), 7.37 (t, $J$ = 7.2 Hz, 2H), 7.24 (t, $J$ = 7.5 Hz, 1H), 7.19 (t, $J$ = 8.4 Hz, 1H), 6.62 (d, $J$ = 8.4 Hz, 2H), 3.92 (s, 6H); $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$): $\delta$ 158.5, 139.2, 132.2, 128.4, 128.0, 126.8, 126.3, 119.8, 114.6, 103.9, 55.7; IR

(neat): $\upsilon_{max}$ 2934, 1584, 1470, 1248, 1106, 976, 749 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{16}H_{16}O_2$ $[M]^+$: 240.1150; found: 240.1157.

**1-(2,6-Dimethoxystyryl)-4-tert-butylbenzene, 14b, Scheme 8**. The same general procedure was followed by using 2,6-dimethoxybenzoic acid (36.5 mg, 0.2 mmol, 1.0 equiv), 4-*tert*-butylstyrene (55 µL, 0.3 mmol, 1.5 equiv), palladium (II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 96:4 hexane/ethyl acetate) afforded the desired product as a white solid (56 mg, 94%), mp 98-100 ºC. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.54 (d, $J$ = 16.8 Hz, 1H), 7.42-7.48 (m, 3H), 7.35 (d, $J$ = 8.4 Hz, 2H), 7.14 (t, $J$ = 8.4 Hz, 1H), 6.58 (d, $J$ = 8.1 Hz, 2H), 3.87 (s, 6H), 1.33 (s, 9H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): $\delta$ 158.6, 149.9, 136.6, 132.2, 127.8, 126.1, 125.4, 119.2, 115.1, 104.0, 55.8, 34.5, 31.3; IR (neat): $\upsilon_{max}$ 2958, 1581, 1470, 1252, 1108, 770 $cm^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{20}H_{24}O_2Na$ $[M + Na]^+$: 319.1674; found: 319.1694.

**1-(2,6-Dimethoxystyryl)-4-fluorobenzene, 14c, Scheme 8**. The same general procedure was followed by using 2,6-dimethoxybenzoic acid (36.5 mg, 0.2 mmol, 1.0 equiv), 4-fluorostyrene (36 µL, 0.3 mmol, 1.5 equiv), palladium (II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 96:4 hexane/ethyl acetate) afforded the desired product as a colourless oil (45 mg, 87%). $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 7.57 (d, $J$ = 16.8 Hz, 1H), 7.51-7.54 (m, 2H), 7.40 (d, $J$ = 16.8 Hz, 1H), 7.20 (t, $J$ = 8.4 Hz, 1H), 7.05 (t, $J$ = 8.4 Hz, 2H), 6.62 (d, $J$ = 8.4 Hz, 2H), 3.92 (s, 6H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): $\delta$ 162.0 (d, $J$ = 244.5 Hz), 158.6, 135.4 (d, $J$ = 3.0 Hz), 131.1, 128.1, 127.8 (d, $J$ = 7.5 Hz), 119.6 (d, $J$ = 1.5 Hz), 115.3 (d, $J$ = 2.1 Hz), 114.6, 104.0, 55.8; $^{19}F$ NMR (470 MHz, $CDCl_3$): $\delta$ -119.0 (s, 1F); IR (neat): $\upsilon_{max}$ 2935, 1590, 1506, 1470, 1246, 1106, 775 $cm^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{16}H_{15}FO_2Na$ $[M + Na]^+$: 281.0954; found: 281.0929.

**1-(2,6-Dimethoxystyryl)-4-chlorobenzene, 14d, Scheme 8**. The same general procedure was followed by using 2,6-dimethoxybenzoic acid (36.5 mg, 0.2 mmol, 1.0 equiv), 4-chlorostyrene (38 µL, 0.3 mmol, 1.5 equiv), palladium (II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 96:4 hexane/ethyl acetate) afforded the desired

product as a colourless oil (45 mg, 82%). $^{1}$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.54 (d, $J$ = 16.8 Hz, 1H), 7.41-7.48 (m, 3H), 7.30 (d, $J$ = 8.4 Hz, 2H), 7.18 (t, $J$ = 8.1 Hz, 1H), 6.60 (d, $J$ = 8.4 Hz, 2H), 3.90 (s, 6H); $^{13}$C{$^{1}$H} NMR (75 MHz, $CDCl_3$): $\delta$ 158.6, 137.8, 132.4, 130.9, 128.6, 128.4, 127.6, 120.5, 114.4, 103.9, 55.8; IR (neat): $\upsilon_{max}$ 2935, 1585, 1484, 1249, 1109, 975, 774 cm$^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{16}H_{15}ClO_2Na$ $[M + Na]^+$: 297.0658; found: 297.0681.

**1-(2,6-Dimethoxystyryl)-4-bromobenzene, 14e, Scheme 8**. The same general procedure was followed by using 2,6-dimethoxybenzoic acid (36.5 mg, 0.2 mmol, 1.0 equiv), 4-bromostyrene (40 µL, 0.3 mmol, 1.5 equiv), palladium (II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 96:4 hexane/ethyl acetate) afforded the desired product as a colourless oil (47 mg, 74%). $^{1}$H NMR (600 MHz, $CDCl_3$): $\delta$ 7.53 (d, $J$ = 16.8 Hz, 1H), 7.46-7.48 (m, 3H), 7.42 (d, $J$ = 8.4 Hz, 2H), 7.20 (t, $J$ = 8.4 Hz, 1H), 6.61 (d, $J$ = 8.4 Hz, 2H), 3.91 (s, 6H); $^{13}$C{$^{1}$H} NMR (150 MHz, $CDCl_3$): $\delta$ 158.6, 138.3, 131.5, 130.9, 128.4, 127.9, 120.6, 120.5, 114.4, 103.9, 55.8; IR (neat): $\upsilon_{max}$ 2935, 1584, 1475, 1249, 1106, 772 cm$^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{16}H_{15}BrO_2Na$ $[M + Na]^+$: 341.0153; found: 341.0155.

**2-(4-Methoxystyryl)-1,3-dimethoxybenzene, 14f, Scheme 8**.[36] The same general procedure was followed by using 2,6-dimethoxybenzoic acid (36.5 mg, 0.2 mmol, 1.0 equiv), 4-vinylanisole (40 µL, 0.3 mmol, 1.5 equiv), palladium (II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 95:5 hexane/ethyl acetate) afforded the desired product as a white solid (32 mg, 60%), mp 71-73 ºC. $^{1}$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.54 (d, $J$ = 16.5 Hz, 1H), 7.49 (d, $J$ = 8.7 Hz, 2H), 7.33 (d, $J$ = 16.5 Hz, 1H), 7.16 (t, $J$ = 8.4 Hz, 1H), 6.90 (d, $J$ = 8.7 Hz, 2H), 6.60 (d, $J$ = 8.4 Hz, 2H), 3.90 (s, 6H), 3.84 (s, 3H); $^{13}$C{$^{1}$H} NMR (75 MHz, $CDCl_3$): $\delta$ 158.8, 158.4, 132.0, 131.8, 127.6, 127.5, 117.8, 114.9, 113.8, 103.9, 55.7, 55.2; IR (neat): $\upsilon_{max}$ 2937, 1601, 1581, 1469, 1249, 1106, 1033, 773 cm$^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{17}H_{18}O_3$ $[M]^+$: 270.1256; found: 270.1257.

**4-(2,6-Dimethoxystyryl)phenyl acetate, 14g, Scheme 8**. The same general procedure was followed by using 2,6-dimethoxybenzoic acid (36.5 mg, 0.2 mmol, 1.0 equiv), 4-

acetoxystyrene (46 µL, 0.3 mmol, 1.5 equiv), palladium (II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 95:5 hexane/ethyl acetate) afforded the desired product as a colourless oil (57 mg, 95%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.54-7.60 (m, 3H), 7.42 (d, $J$ = 16.5 Hz, 1H), 7.19 (t, $J$ = 8.4 Hz, 1H), 7.08 (d, $J$ = 8.4 Hz, 2H), 6.61 (d, $J$ = 8.4 Hz, 2H), 3.91 (s, 6H), 2.32 (s, 3H); $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$): $\delta$ 171.3, 160.1, 151.3, 138.9, 133.0, 129.9, 129.0, 123.3, 122.0, 116.3, 105.7, 57.5, 22.9; IR (neat): $\upsilon_{max}$ 2937, 1760, 1584, 1504, 1195, 1105, 772 cm$^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{18}H_{18}O_4Na$ $[M + Na]^+$: 321.1103; found: 321.1115.

**1-(2,6-Dimethoxystyryl)-3-nitrobenzene, 14h, Scheme 8**. The same general procedure was followed by using 2,6-dimethoxybenzoic acid (36.5 mg, 0.2 mmol, 1.0 equiv), 3-nitrostyrene (42 µL, 0.3 mmol, 1.5 equiv), palladium (II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv.). Column chromatography ($SiO_2$, eluting with 95:5 hexane/ethyl acetate) afforded the desired product as a yellow solid (53 mg, 93%), mp 116-118 ºC. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.37 (s, 1H), 8.04-8.06 (m, 1H), 7.83 (d, $J$ = 7.8 Hz, 1H), 7.59-7.66 (m, 2H), 7.49 (t, $J$ = 8.4 Hz, 1H), 7.23 (t, $J$ = 8.4 Hz, 1H), 6.62 (d, $J$ = 8.4 Hz, 2H), 3.93 (s, 3H); $^{13}$C{$^1$H} NMR (150 MHz, $CDCl_3$): $\delta$ 158.8, 148.6, 141.2, 132.0, 129.6, 129.2, 129.1, 122.9, 121.3, 120.9, 113.7, 103.9, 55.8; IR (neat): $\upsilon_{max}$ 1527, 1473, 1343, 1107, 737 cm$^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{16}H_{15}NO_4$ $[M]^+$: 285.1001; found: 285.1013.

**(*E*)-1-(2,6-Dimethoxyphenyl)-2-(3,5-dimethoxyphenyl)ethene, 14i, Scheme 8**. The same general procedure was followed by using 2,6-dimethoxybenzoic acid (36.5 mg, 0.2 mmol, 1.0 equiv), 3,5-dimethoxystyrene (49 mg, 0.3 mmol, 1.5 equiv), palladium (II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (50 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a colourless oil (45 mg, 84%). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 7.53 (d, $J$ = 16.8 Hz, 1H), 7.46 (d, $J$ = 16.8 Hz, 1H), 7.19 (t, $J$ = 8.4 Hz, 1H), 6.73 (d, $J$ = 1.8 Hz, 2H), 6.61 (d, $J$ = 8.4 Hz, 2H), 6.40 (t, $J$ = 2.4 Hz, 1H), 3.91 (s, 6H), 3.86 (s, 6H); $^{13}$C{$^1$H} NMR (150 MHz, $CDCl_3$): $\delta$ 160.8, 158.6, 141.4, 132.3, 128.2, 120.4, 114.6, 104.5, 104.0, 99.4, 55.8, 55.3; IR (neat): $\upsilon_{max}$ 2937, 2838, 1587, 1472,

1153, 773 $cm^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{18}H_{20}O_4Na$ $[M + Na]^+$: 323.1259; found: 323.1278.

**2-(2,6-Dimethoxystyryl)naphthalene, 14j, Scheme 8**. The same general procedure was followed by using 2,6-dimethoxybenzoic acid (36.5 mg, 0.2 mmol, 1.0 equiv), 2-vinylnaphthalene (46 mg, 0.3 mmol, 1.5 equiv), palladium (II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 96:4 hexane/ethyl acetate) afforded the desired product as a white solid (50 mg, 86%), mp 136-138 ºC. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.75-7.87 (m, 6H), 7.62 (d, $J$ = 16.8 Hz, 1H), 7.40-7.49 (m, 2H), 7.20 (t, $J$ = 8.4 Hz, 1H), 6.63 (d, $J$ = 8.4 Hz, 2H), 3.94 (s, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): $\delta$ 158.7, 136.9, 133.9, 132.9, 132.4, 128.2, 128.0, 127.96, 127.7, 126.2, 126.1, 125.4, 123.8, 120.4, 114.9, 104.1, 55.8; IR (neat): $\upsilon_{max}$ 1583, 1470, 1242, 1105, 772 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{20}H_{18}O_2$ $[M]^+$: 290.1307; found: 290.1310.

**1-(2,6-Dimethoxystyryl)-2,3,4,5,6-pentafluorobenzene, 14k, Scheme 8**. The same general procedure was followed by using 2,6-dimethoxybenzoic acid (36.5 mg, 0.2 mmol, 1.0 equiv), pentafluorostyrene (42 µL, 0.3 mmol, 1.5 equiv), palladium (II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 96:4 hexane/ethyl acetate) afforded the desired product as a white solid (56 mg, 85%), mp 146-148 ºC. $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 7.75 (d, $J$ = 17.4 Hz, 1H), 7.47 (d, $J$ = 16.8 Hz, 1H), 7.24 (t, $J$ = 8.4 Hz, 1H), 6.61 (d, $J$ = 8.4 Hz, 2H), 3.92 (s, 6H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): $\delta$ 158.9, 144.6 (dm, $J$ = 249.0 Hz), 139.1, (dm, $J$ = 250.5 Hz), 137.7 (dm, $J$ = 247.5 Hz), 129.6, 128.6 (t, $J$ = 9.0 Hz), 116.2, 114.2 (td, $J$ = 13.5 Hz, 4.5 Hz), 113.8, 103.8, 55.8 (d, $J$ = 3.0 Hz); $^{19}F$ NMR (470 MHz, $CDCl_3$): $\delta$ -144.6 (dd, $J$ = 26.8 Hz, 8.9 Hz, 2F), -159.5 (t, $J$ = 26.3 Hz, 1F), -165.0 (td, $J$ = 26.3 Hz, 8.9 Hz, 2F); IR (neat): $\upsilon_{max}$ 1585, 1496, 1245, 1108, 1000, 774 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{16}H_{11}F_5O_2$ $[M]^+$: 330.0679; found: 330.0665.

**2-(2-Methoxystyryl)-1,3-dimethoxybenzene, 14l, Scheme 8**. The same general procedure was followed by using 2,6-dimethoxybenzoic acid (36.5 mg, 0.2 mmol, 1.0 equiv), 2-vinylanisole (40 µL, 0.3 mmol, 1.5 equiv), palladium (II) trifluoroacetate (6.7

mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 96:4 hexane/ethyl acetate) afforded the desired product as a white solid (41 mg, 76%), mp 66-68 ºC. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.87 (d, $J$ = 16.8 Hz, 1H), 7.64 (dd, $J$ = 7.5 Hz, 0.9 Hz, 1H), 7.39 (d, $J$ = 16.8 Hz, 1H), 7.11-7.25 (m, 2H), 6.96 (t, $J$ = 7.5 Hz, 1H), 6.87 (d, $J$ = 8.1 Hz, 1H), 6.58 (d, $J$ = 8.4 Hz, 2H), 3.88 (s, 6H), 3.86 (s, 3H); $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$): $\delta$ 158.6, 156.7, 128.6, 128.0, 127.8, 127.2, 126.2, 120.7, 120.4, 115.4, 110.8, 104.0, 55.8, 55.6; IR (neat): $\upsilon_{max}$ 2935, 2837, 1586, 1468, 1243, 1106, 746 cm$^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{17}H_{18}O_3Na$ [M + Na]$^+$: 293.1154; found: 293.1147.

**1,4-Bis(2,6-dimethoxystyryl)benzene, 14m, Scheme 8**. The same general procedure was followed by using 2,6-dimethoxybenzoic acid (36.5 mg, 0.2 mmol, 1.0 equiv), 1,4-divinylbenzene (22 µL, 0.15 mmol, 0.75 equiv), palladium (II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a yellow solid (29 mg, 72%), mp 180-182 ºC. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 7.61 (d, $J$ = 16.2 Hz, 2H), 7.54 (s, 4H), 7.50 (d, $J$ = 16.8 Hz, 2H), 7.18 (t, $J$ = 8.4 Hz, 2H), 6.62 (d, $J$ = 8.4 Hz, 4H), 3.93 (s, 12H); $^{13}$C{$^1$H} NMR (150 MHz, $CDCl_3$): $\delta$ 158.6, 138.0, 132.2, 127.9, 126.5, 119.3, 115.0, 104.0, 55.8; IR (neat): $\upsilon_{max}$ 1582, 1472, 1251, 1105, 770 cm$^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{26}H_{26}O_4$ [M]$^+$: 402.1831; found: 402.1833.

**(*E*)-3-(2,6-Dimethoxyphenyl)acrylonitrile, 14n, Scheme 8**. The same general procedure was followed by using 2,6-dimethoxybenzoic acid (36.5 mg, 0.2 mmol, 1.0 equiv), acrylonitrile (20 µL, 0.3 mmol, 1.5 equiv), palladium (II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a colourless oil (24 mg, 64%). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 7.82 (d, $J$ = 16.8 Hz, 1H), 7.28-7.34 (m, 2H), 7.22 (d, $J$ = 12.0 Hz, 1H), 6.59 (d, $J$ = 8.4 Hz, 2H), 6.57 (d, $J$ = 8.4 Hz, 2H), 6.42 (d, $J$ = 16.8 Hz, 1H), 5.58 (d, $J$ = 12.0 Hz, 1H), 3.89 (s, 12H); $^{13}$C{$^1$H} NMR (150 MHz, $CDCl_3$): $\delta$ 158.8, 158.2, 141.4, 141.0, 132.0, 131.6, 120.2, 117.3, 111.9, 111.6, 103.7, 103.6, 99.9, 98.4, 55.8, 55.4; IR (neat): $\upsilon_{max}$ 2936, 2210,

1696, 1601, 1475, 1249, 1112, 777 $cm^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{11}H_{11}NO_2Na$ $[M + Na]^+$: 212.0687; found: 212.0691.

**(*E*)-Methyl 3-(2,6-dimethoxyphenyl)acrylate, 14o, Scheme 8**.[13] The same general procedure was followed by using 2,6-dimethoxybenzoic acid (36.5 mg, 0.2 mmol, 1.0 equiv), methyl acrylate (27 µL, 0.3 mmol, 1.5 equiv), palladium (II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a white solid (36 mg, 81%), mp 70-72 ºC. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 8.14 (d, *J* = 16.2 Hz, 1H), 7.26 (t, *J* = 8.4 Hz, 1H), 6.88 (d, *J* = 16.2 Hz, 1H), 6.55 (d, *J* = 8.4 Hz, 2H), 3.87 (s, 6H), 3.79 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): $\delta$ 169.0, 160.0, 135.6, 131.2, 120.2, 112.1, 103.6, 55.7, 51.4; IR (neat): $\upsilon_{max}$ 2942, 1703, 1618, 1255, 1161, 1104, 748 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{12}H_{14}O_4$ $[M]^+$: 222.0892; found: 222.0902.

**(*E*)-Butyl 3-(2,6-dimethoxyphenyl)acrylate, 14p, Scheme 8**. The same general procedure was followed by using 2,6-dimethoxybenzoic acid (36.5 mg, 0.2 mmol, 1.0 equiv), butyl acrylate (43 µL, 0.3 mmol, 1.5 equiv), palladium (II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a colourless oil (39 mg, 74%). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 8.14 (d, *J* = 16.2 Hz, 1H), 7.26 (t, *J* = 8.4 Hz, 1H), 6.88 (d, *J* = 16.5 Hz, 1H), 6.55 (d, *J* = 8.4 Hz, 2H), 4.20 (t, *J* = 6.6 Hz, 2H), 3.88 (s, 6H), 1.64-1.74 (m, 2H), 1.38-1.50 (m, 2H), 0.96 (t, *J* = 7.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): $\delta$ 168.6, 159.8, 135.2, 131.0, 120.5, 112.1, 103.5, 63.9, 55.6, 30.8, 19.1, 13.7; IR (neat): $\upsilon_{max}$ 2959, 1706, 1623, 1587, 1474, 1255, 1109, 744 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{15}H_{20}O_4$ $[M]^+$: 264.1362; found: 264.1346.

**(*E*)-Phenyl 3-(2,6-dimethoxyphenyl)acrylate, 14q, Scheme 8**. The same general procedure was followed by using 2,6-dimethoxybenzoic acid (36.5 mg, 0.2 mmol, 1.0 equiv), phenyl acrylate (45 mg, 0.3 mmol, 1.5 equiv), palladium (II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 9:1 hexane/ethyl acetate) afforded the desired

product as a white solid (41.5 mg, 73%), mp 106-108 ºC. $^{1}$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.36 (d, $J$ = 16.2 Hz, 1H), 7.42 (t, $J$ = 7.8 Hz, 2H), 7.33 (t, $J$ = 8.4 Hz, 1H), 7.26 (d, $J$ = 8.1 Hz, 1H), 7.20 (d, $J$ = 7.5 Hz, 2H), 7.11 (d, $J$ = 16.2 Hz, 1H), 6.61 (d, $J$ = 8.4 Hz, 2H), 3.93 (s, 6H); $^{13}$C{$^{1}$H} NMR (75 MHz, $CDCl_3$): $\delta$ 167.0, 160.2, 151.2, 137.4, 131.8, 129.4, 125.5, 121.9, 119.6, 112.1, 103.7, 55.8; IR (neat): $\upsilon_{max}$ 1735, 1619, 1478, 1254, 1131, 738 cm$^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{17}H_{16}O_4Na$ [M + Na]$^{+}$: 307.0946; found: 307.0957.

**(*E*)-Methyl 3-(2,6-dimethoxyphenyl)-2-methylacrylate, 14r, Scheme 8**.[37] The same general procedure was followed by using 2,6-dimethoxybenzoic acid (36.5 mg, 0.2 mmol, 1.0 equiv), methyl methacrylate (32 µL, 0.3 mmol, 1.5 equiv), palladium (II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a colourless oil (19 mg, 40%). $^{1}$H NMR (600 MHz, $CDCl_3$): $\delta$ 7.54 (s, 1H), 7.28 (t, $J$ = 8.4 Hz, 1H), 6.59 (d, $J$ = 8.4 Hz, 2H), 3.83 (s, 6H), 3.81 (s, 3H), 1.79 (d, $J$ = 1.2 Hz, 3H); $^{13}$C{$^{1}$H} NMR (150 MHz, $CDCl_3$): $\delta$ 168.7, 157.7, 131.9, 130.9, 129.7, 113.4, 103.5, 55.6, 51.8, 15.2; IR (neat): $\upsilon_{max}$ 2950, 2840, 1710, 1587, 1470, 1253, 1105, 745 cm$^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{13}H_{16}O_4Na$ [M + Na]$^{+}$: 259.0946; found: 259.0934.

**1-((*E*)-3-(2,6-Dimethoxyphenyl)prop-1-enyl)benzene, 14s, Scheme 8**. The same general procedure was followed by using 2,6-dimethoxybenzoic acid (36.5 mg, 0.2 mmol, 1.0 equiv), allylbenzene (40 µL, 0.3 mmol, 1.5 equiv), palladium (II) trifluoroacetate (13.4 mg, 0.04 mmol, 0.1 equiv), and 1,4-benzoquinone (65 mg, 0.4 mmol, 3.0 equiv). Column chromatography ($SiO_2$, eluting with 95:5 hexane/ethyl acetate) afforded the desired product as a colourless oil (28 mg, 55%). $^{1}$H NMR (600 MHz, $CDCl_3$): $\delta$ 7.33 (d, $J$ = 7.2 Hz, 2H), 7.25-7.28 (m, 2H), 7.13-7.20 (m, 2H), 7.09 (d, $J$ = 8.4 Hz, 2H), 6.32-6.41 (m, 2H), 3.85 (s, 6H), 3.58 (d, $J$ = 6.0 Hz, 2H); $^{13}$C{$^{1}$H} NMR (150 MHz, $CDCl_3$): $\delta$ 158.2, 138.1, 129.4, 129.0, 128.3, 127.1, 126.5, 126.0, 116.5, 103.8, 55.8, 26.4; IR (neat): $\upsilon_{max}$ 2927, 1728, 1593, 1469, 1254, 1110, 729 cm$^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{17}H_{18}O_2Na$ [M + Na]$^{+}$: 277.1204; found: 277.1179.

**1-Fluoro-4-((*E*)-3-(2,6-dimethoxyphenyl)prop-1-enyl)benzene, 14t, Scheme 8**. The same general procedure was followed by using 2,6-dimethoxybenzoic acid (36.5 mg, 0.2 mmol, 1.0 equiv), 4-fluoroallylbenzene (41 µL, 0.3 mmol, 1.5 equiv), palladium (II) trifluoroacetate (13.4 mg, 0.04 mmol, 0.1 equiv), and 1,4-benzoquinone (65 mg, 0.4 mmol, 3.0 equiv). Column chromatography ($SiO_2$, eluting with 95:5 hexane/ethyl acetate) afforded the desired product as a white solid (31 mg, 57%), mp 68-70 ºC. $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 7.28-7.31 (m, 2H), 7.19 (t, $J$ = 8.4 Hz, 1H), 6.96 (t, $J$ = 8.4 Hz, 2H), 6.60 (d, $J$ = 8.4 Hz, 2H), 6.36 (d, $J$ = 15.6 Hz, 1H), 6.25-6.30 (m, 1H), 3.86 (s, 6H), 3.58 (d, $J$ = 6.0 Hz, 2H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): $\delta$ 161.7 (d, $J$ = 243.0 Hz), 158.2, 134.2 (d, $J$ = 3.0 Hz), 128.7 (d, $J$ = 3.0 Hz), 128.3, 127.3 (d, $J$ = 7.5 Hz), 127.2, 116.4, 115.1 (d, $J$ = 21.0 Hz), 103.8, 55.8, 26.4; $^{19}F$ NMR (470 MHz, $CDCl_3$): $\delta$ -119.6 (s, 1F); IR (neat): $\upsilon_{max}$ 2929, 1592, 1470, 1255, 1107, 839 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{17}H_{17}FO_2$ $[M]^+$: 272.1213; found: 272.1208.

**2-(4-Methoxycinnamyl)-1,3-dimethoxybenzene, 14u, Scheme 8**.[12] The same general procedure was followed by using 2,6-dimethoxybenzoic acid (36.5 mg, 0.2 mmol, 1.0 equiv), 4-methoxyallylbenzene (46 µL, 0.3 mmol, 1.5 equiv), palladium (II) trifluoroacetate (13.4 mg, 0.04 mmol, 0.1 equiv), and 1,4-benzoquinone (65 mg, 0.4 mmol, 3.0 equiv). Column chromatography ($SiO_2$, eluting with 95:5 hexane/ethyl acetate) afforded the desired product as a white solid (24 mg, 42%), mp 70-72 ºC. $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 7.26 (d, $J$ = 9.0 Hz, 2H), 7.17 (t, $J$ = 8.4 Hz, 1H), 6.81 (d, $J$ = 8.4 Hz, 2H), 6.58 (d, $J$ = 8.4 Hz, 2H), 6.34 (d, $J$ = 15.6 Hz, 1H), 6.18-6.23 (m, 1H), 3.85 (s, 6H), 3.79 (s, 3H), 3.55 (d, $J$ = 6.6 Hz, 2H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): $\delta$ 158.4, 158.2, 131.1, 128.8, 127.05, 127.02, 126.8, 116.8, 113.7, 103.8, 55.8, 55.2, 26.4; IR (neat): $\upsilon_{max}$ 2930, 1597, 1510, 1469, 1250, 1111, 833 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{18}H_{20}O_3$ $[M]^+$: 284.1412; found: 284.1408.

**2,6-Dimethoxycinnamyl acetate, 14v, Scheme 8**.[12] The same general procedure was followed by using 2,6-dimethoxybenzoic acid (36.5 mg, 0.2 mmol, 1.0 equiv), allylacetate (33 µL, 0.3 mmol, 1.5 equiv), palladium (II) trifluoroacetate (13.4 mg, 0.04 mmol, 0.1 equiv), and 1,4-benzoquinone (65 mg, 0.6 mmol, 3.0 equiv). Column chromatography ($SiO_2$, eluting with 9:1 hexane/ethyl acetate) afforded the desired

product as a colourless oil (32 mg, 67%). $^{1}$H NMR (600 MHz, $CDCl_3$): $\delta$ 7.18 (t, $J$ = 8.4 Hz, 1H), 6.99 (d, $J$ = 16.2 Hz, 1H), 6.71-6.76 (m, 1H), 6.56 (d, $J$ = 8.4 Hz, 2H), 4.75 (dd, $J$ = 6.6 Hz, 0.6 Hz, 2H), 3.86 (s, 6H), 2.11 (s, 3H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): $\delta$ 171.0, 158.6, 128.6, 126.8, 125.0, 113.3, 103.8, 67.1, 55.7, 21.1; IR (neat): $\upsilon_{max}$ 2938, 1737, 1587, 1472, 1247, 772 $cm^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{13}H_{16}O_4Na$ $[M + Na]^+$: 259.0946; found: 259.0923.

**3-(2,6-Dimethoxyphenyl)-1-phenylpropan-1-one, 14w, Scheme 8**.[21b] The same general procedure was followed by using 2,6-dimethoxybenzoic acid (36.5 mg, 0.2 mmol, 1.0 equiv), 1-phenylprop-2-en-1-ol (40 µL, 0.3 mmol, 1.5 equiv), palladium (II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv) except the reaction was run for 48 h. Column chromatography ($SiO_2$, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a white solid (20.5 mg, 38%), mp 88-90 ºC. $^{1}$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.02 (dd, $J$ = 8.4 Hz, 1.2 Hz, 2H), 7.54-7.57 (m, 1H), 7.45-7.47 (m, 2H), 7.18 (t, $J$ = 8.4 Hz, 1H), 6.57 (d, $J$ = 8.4 Hz, 2H), 3.81 (s, 6H), 3.14-3.17 (m, 2H), 3.08-3.11 (m, 2H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): $\delta$ 200.6, 158.2, 137.0, 132.7, 128.4, 128.2, 127.1, 117.4, 103.5, 55.6, 38.3, 18.5; IR (neat): $\upsilon_{max}$ 2937, 1682, 1593, 1471, 1254, 1107, 778, 693 $cm^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{17}H_{18}O_3Na$ $[M + Na]^+$: 293.1154; found: 293.1130.

**Diethyl 2-(2,6-dimethoxycinnamyl)malonate, 14x, Scheme 8**.[12] The same general procedure was followed by using 2,6-dimethoxybenzoic acid (36.5 mg, 0.2 mmol, 1.0 equiv), diethyl 2-allylmalonate (60 µL, 0.3 mmol, 1.5 equiv), palladium (II) trifluoroacetate (13.4 mg, 0.04 mmol, 0.1 equiv), and 1,4-benzoquinone (65 mg, 0.6 mmol, 3.0 equiv). Column chromatography ($SiO_2$, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a colourless oil (44 mg, 65%). $^{1}$H NMR (600 MHz, $CDCl_3$): $\delta$ 7.12 (t, $J$ = 8.4 Hz, 1H), 6.74 (t, $J$ = 16.2 Hz, 1H), 6.51-6.58 (m, 3H), 4.19-4.26 (m, 4H), 3.82 (s, 6H), 3.51 (t, $J$ = 7.8 Hz, 1H), 2.83 (td, $J$ = 7.8 Hz, 1.2 Hz, 2H), 1.28 (t, $J$ = 6.6 Hz, 6H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): $\delta$ 169.1, 158.2, 129.7, 127.7, 123.0, 114.4, 103.9, 61.3, 55.6, 52.5, 34.0, 14.0; IR (neat): $\upsilon_{max}$ 2981, 1732, 1585, 1472, 1251, 1113, 772 $cm^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{18}H_{24}O_6Na$ $[M + Na]^+$: 359.1471; found: 359.1468.

**(E)-4-Methoxybenzyl 5-(2,6-dimethoxyphenyl)pent-4-enoate, 14y, Scheme 8**. The same general procedure was followed by using 2,6-dimethoxybenzoic acid (36.5 mg, 0.2 mmol, 1.0 equiv), 4-methoxybenzyl pent-4-enoate (66 mg, 0.3 mmol, 1.5 equiv), palladium (II) trifluoroacetate (13.4 mg, 0.04 mmol, 0.1 equiv), and 1,4-benzoquinone (65 mg, 0.6 mmol, 3.0 equiv). Column chromatography ($SiO_2$, eluting with 8:2 hexane/ethyl acetate) afforded the desired product as colourless oil (28.5 mg, 40%). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 7.31 (d, $J$ = 8.4 Hz, 2H), 7.13 (t, $J$ = 8.4 Hz, 1H), 6.88 (d, $J$ = 8.4 Hz, 2H), 6.70 (d, $J$ = 16.2 Hz, 1H), 6.57-6.62 (m, 1H), 6.56 (d, $J$ = 8.4 Hz, 2H), 5.08 (s, 2H), 3.83 (s, 6H), 3.82 (s, 3H), 2.58-2.61 (m, 2H), 2.53-2.56 (m, 2H); $^{13}$C{$^1$H} NMR (150 MHz, $CDCl_3$): $\delta$ 173.2, 159.5, 158.2, 132.7, 130.0, 128.2, 127.5, 121.2, 114.6, 113.9, 103.9, 65.9, 55.7, 55.2, 34.5, 30.0; IR (neat): $\upsilon_{max}$ 2928, 1732, 1586, 1514, 1469, 1248, 1111, 823 cm$^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{21}H_{24}O_5Na$ [M + Na]$^+$: 379.1521; found: 379.1530.

**1-(2,6-Diethoxystyryl)benzene, 14z, Scheme 8**. The same general procedure was followed by using 2,6-diethoxybenzoic acid (42 mg, 0.2 mmol, 1.0 equiv), styrene (35 µL, 0.3 mmol, 1.5 equiv), palladium (II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 95:5 hexane/ethyl acetate) afforded the desired product as a white solid (48 mg, 90%), mp 55-57 ºC. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.72 (d, $J$ = 16.5 Hz, 1H), 7.50-7.56 (m, 3H), 7.36 (t, $J$ = 7.5 Hz, 2H), 7.21-7.26 (m, 1H), 7.13 (t, $J$ = 8.4 Hz, 1H), 6.57 (d, $J$ = 8.4 Hz, 2H), 4.12 (q, $J$ = 6.9 Hz, 4H), 1.51 (t, $J$ = 7.2 Hz, 6H); $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$): $\delta$ 158.1, 139.5, 132.1, 128.4, 128.0, 126.8, 126.3, 120.2, 114.8, 104.9, 64.2, 14.9; IR (neat): $\upsilon_{max}$ 2978, 1582, 1458, 1247, 1116, 1083, 748 cm$^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{18}H_{20}O_2Na$ [M + Na]$^+$: 291.1361; found: 291.1352.

**1-((3-(Benzyloxy)-2-styrylphenoxy)methyl)benzene, 14aa, Scheme 8**. The same general procedure was followed by using 2,6-dibenzyloxybenzoic acid (67 mg, 0.2 mmol, 1.0 equiv), styrene (35 µL, 0.3 mmol, 1.5 equiv), palladium (II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 95:5 hexane/ethyl acetate) afforded the desired product as a white solid (59 mg, 75%), mp 88-90 ºC. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 7.70

(d, *J* = 16.8 Hz, 1H), 7.62 (d, *J* = 16.8 Hz, 1H), 7.51 (d, *J* = 7.8 Hz, 4H), 7.41-7.43 (m, 6H), 7.36 (t, *J* = 7.8 Hz, 2H), 7.32 (t, *J* = 7.8 Hz, 2H), 7.21 (t, *J* = 7.2 Hz, 1H), 7.14 (t, *J* = 7.8 Hz, 1H), 6.68 (d, *J* = 8.4 Hz, 2H), 5.19 (s, 4H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): $\delta$ 157.8, 139.2, 137.1, 132.7, 128.5, 128.4, 127.9, 127.8, 127.2, 126.9, 126.3, 119.7, 115.8, 105.9, 70.8; IR (neat): $\upsilon_{max}$ 2926, 1728, 1582, 1452, 1254, 1104, 741 $cm^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{28}H_{24}O_2Na$ $[M + Na]^+$: 415.1674; found: 415.1674.

**1,3,5-Trimethoxy-2-styrylbenzene, 14ab, Scheme 8**.[38] The same general procedure was followed by using 2,4,6-trimethoxybenzoic acid (42.5 mg, 0.2 mmol, 1.0 equiv), styrene (35 µL, 0.3 mmol, 1.5 equiv), palladium (II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a colourless oil (50 mg, 93%). $^{1}H$ NMR (600 MHz, $CDCl_3$): $\delta$ 7.55 (d, *J* = 7.8 Hz, 2H), 7.50 (d, *J* = 16.2 Hz, 1H), 7.44 (d, *J* = 16.2 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 2H), 7.22 (t, *J* = 7.2 Hz, 1H), 6.20 (s, 2H), 3.91 (s, 6H), 3.86 (s, 3H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): $\delta$ 160.2, 159.5, 139.7, 129.9, 128.4, 126.5, 126.1, 119.8, 108.1, 90.8, 55.8, 55.3; IR (neat): $\upsilon_{max}$ 2938, 1597, 1461, 1328, 1210, 1119, 813 $cm^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{17}H_{18}O_3Na$ $[M + Na]^+$: 293.1154; found: 293.1140.

**2-(4-Phenylstyryl)-1,3,5-trimethoxybenzene, 14ac, Scheme 8**. The same general procedure was followed by using 2,4,6-trimethoxybenzoic acid (42.5 mg, 0.2 mmol, 1.0 equiv), 4-vinylbiphenyl (54 mg, 0.3 mmol, 1.5 equiv), palladium (II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a white solid (57 mg, 82%), mp 150-152 ºC. $^{1}H$ NMR (600 MHz, $CDCl_3$): $\delta$ 7.64-7.66 (m, 2H), 7.59-7.62 (m, 4H), 7.53 (d, *J* = 16.8 Hz, 1H), 7.45-7.49 (m, 3H), 7.35 (t, *J* = 7.2 Hz, 1H), 6.21 (s, 2H), 3.92 (s, 6H), 3.87 (s, 3H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): $\delta$ 160.3, 159.6, 141.0, 139.1, 138.8, 129.3, 128.7, 127.1, 127.0, 126.8, 126.6, 120.0, 108.2, 90.8, 55.8, 55.3; IR (neat): $\upsilon_{max}$ 1592, 1458, 1326, 1218, 1153, 1119, 766 $cm^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{23}H_{22}O_3Na$ $[M + Na]^+$: 369.1467; found: 369.1467.

**2-(2-Methylstyryl)-1,3,5-trimethoxybenzene, 14ad, Scheme 8**.[39] The same general procedure was followed by using 2,4,6-trimethoxybenzoic acid (42.5 mg, 0.2 mmol, 1.0

equiv), 2-methylstyrene (39 µL, 0.3 mmol, 1.5 equiv), palladium (II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a white solid (51 mg, 90%), mp 86-88 ºC. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.62-7.69 (m, 2H), 7.24 (d, $J$ = 16.5 Hz, 1H), 7.08-7.19 (m, 3H), 6.17 (s, 2H), 3.87 (s, 6H), 3.84 (s, 3H), 2.39 (s, 3H); $^{13}$C{$^1$H} NMR (150 MHz, $CDCl_3$): $\delta$ 160.2, 159.4, 138.7, 135.3, 130.1, 128.0, 126.5, 126.0, 124.9, 120.8, 108.6, 90.8, 55.8, 55.3, 20.0; IR (neat): $\upsilon_{max}$ 2936, 1586, 1460, 1198, 1118, 809 cm$^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{18}H_{20}O_3Na$ $[M + Na]^+$: 307.1310; found: 307.1308.

**2-(3-Chlorostyryl)-1,3,5-trimethoxybenzene, 14ae, Scheme 8**.[39] The same general procedure was followed by using 2,4,6-trimethoxybenzoic acid (42.5 mg, 0.2 mmol, 1.0 equiv), 3-chlorostyrene (38 µL, 0.3 mmol, 1.5 equiv), palladium (II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a white solid (55 mg, 91%), mp 80-82 ºC. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 7.51 (t, $J$ = 1.8 Hz, 1H), 7.42 (d, $J$ = 1.8 Hz, 2H), 7.38 (d, $J$ = 7.8 Hz, 1H), 7.25 (t, $J$ = 7.8 Hz, 1H), 7.15-7.17 (m, 1H), 6.19 (s, 2H), 3.90 (s, 6H), 3.86 (s, 3H); $^{13}$C{$^1$H} NMR (150 MHz, $CDCl_3$): $\delta$ 160.5, 159.6, 141.7, 134.3, 129.5, 128.2, 126.2, 125.9, 124.3, 121.2, 107.6, 90.7, 55.7, 55.3; IR (neat): $\upsilon_{max}$ 2961, 1586, 1462, 1326, 1220, 1117, 962, 796 cm$^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{17}H_{17}ClO_3Na$ $[M + Na]^+$: 327.0764; found: 327.0783.

**4-(2,4,6-Trimethoxystyryl)-2-methoxyphenyl acetate, 14af, Scheme 8**. The same general procedure was followed by using 2,4,6-trimethoxybenzoic acid (42.5 mg, 0.2 mmol, 1.0 equiv), 4-acetoxy-3-methoxystyrene (57 mg, 0.3 mmol, 1.5 equiv), palladium (II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 8:2 hexane/ethyl acetate) afforded the desired product as a white solid (61 mg, 85%), mp 105-107 ºC. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 7.43 (d, $J$ = 16.8 Hz, 1H), 7.33 (d, $J$ = 16.2 Hz, 1H), 7.10-7.11 (m, 2H), 7.00 (d, $J$ = 8.4 Hz, 1H), 6.19 (s, 2H), 3.898 (s, 3H), 3.896 (s, 6H), 3.86 (s, 3H), 2.33 (s, 3H); $^{13}$C{$^1$H} NMR (150 MHz, $CDCl_3$): $\delta$ 169.2, 160.3, 159.5, 150.9, 138.9, 138.4, 129.3, 122.6, 120.2, 118.6, 110.0, 107.9, 90.8, 55.9, 55.8, 55.3, 20.7; IR (neat): $\upsilon_{max}$

2933, 1761, 1598, 1460, 1118, 817 $cm^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{20}H_{22}O_6Na$ $[M + Na]^+$: 381.1314; found: 381.1336.

**(*E*)-Butyl 3-(2,4,6-trimethoxyphenyl)acrylate, 14ag, Scheme 8**.[40] The same general procedure was followed by using 2,4,6-trimethoxybenzoic acid (42.5 mg, 0.2 mmol, 1.0 equiv), butyl acrylate (43 µL, 0.3 mmol, 1.5 equiv), palladium (II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 8:2 hexane/ethyl acetate) afforded the desired product as a white solid (41 mg, 70%), mp 79-81 ºC. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 8.09 (d, $J$ = 16.2 Hz, 1H), 6.75 (d, $J$ = 16.2 Hz, 1H), 6.11 (s, 2H), 4.19 (t, $J$ = 6.6 Hz, 2H), 3.87 (s, 6H), 3.84 (s, 3H), 1.64-1.73 (m, 2H), 1.37-1.50 (m, 2H), 0.96 (t, $J$ = 7.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): $\delta$ 169.1, 162.6, 161.1, 135.4, 117.4, 105.7, 90.3, 63.8, 55.6, 55.3, 30.9, 19.2, 13.8; IR (neat): $\upsilon_{max}$ 2939, 1699, 1602, 1461, 1156, 1119, 815 $cm^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{16}H_{22}O_5Na$ $[M + Na]^+$: 317.1365; found: 317.1360.

**Diethyl 2-(2,4,6-trimethoxycinnamyl)malonate, 14ah, Scheme 8**. The same general procedure was followed by using 2,4,6-trimethoxybenzoic acid (42.5 mg, 0.2 mmol), diethyl 2-allylmalonate (60 µL, 0.3 mmol, 1.5 equiv.), palladium (II) trifluoroacetate (13.4 mg, 0.04 mmol, 0.1 equiv.), and 1,4-benzoquinone (65 mg, 0.6 mmol, 3.0 equiv.). Column chromatography ($SiO_2$, eluting with 8:2 hexane/ethyl acetate) afforded the desired product as a colourless oil (45 mg, 62%). $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 6.66 (d, $J$ = 16.2 Hz, 1H), 6.38-6.43 (m, 1H), 6.12 (s, 2H), 4.18-4.23 (m, 4H), 3.81 (s, 3H), 3.80 (s, 6H), 3.48 (t, $J$ = 7.8 Hz, 1H), 2.80 (t, $J$ = 7.8 Hz, 2H), 1.27 (t, $J$ = 7.2 Hz, 6H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): $\delta$ 169.2, 159.8, 159.0, 127.2, 122.8, 107.7, 90.6, 61.2, 55.6, 55.2, 52.6, 34.0, 14.0; IR (neat): $\upsilon_{max}$ 2939, 1729, 1604, 1462, 1124, 1036, 814 $cm^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{19}H_{26}O_7Na$ $[M + Na]^+$: 389.1576; found: 389.1563.

**General experimental procedure for the decarboxylative Heck reaction between electron-deficient carboxylic acids and vinyl arenes**

To an oven-dried 15 mL sealed tube, a mixture of pentafluorobenzoic acid (0.20-0.24 mmol, 1.0-1.2 equiv), palladium(II)trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and silver carbonate (110 mg, 0.4 mmol, 2.0 equiv) was taken then dry DMF (3.0 mL) was

added to it. After purging with nitrogen, the corresponding styrenes (0.20-0.30 mmol, 1.0-1.5 equiv) were added via microliter syringe and the vessel was sealed with a screw cap. The reaction mixture was allowed to stir for 16 h at room temperature. After completion (as detected by TLC), the reaction mixture was poured into water (20 mL) and extracted with ethyl acetate (30 mL). The organic layer was washed with water (10 mL x 2) and brine (10 mL), dried over anhydrous $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography using ethyl acetate/hexane as eluent to afford the desired product.

**1,2,3,4,5-Pentafluoro-6-styrylbenzene, 17a, Scheme 9**.[32] The same general procedure was followed by using pentafluorobenzoic acid (42.5 mg, 0.2 mmol, 1.0 equiv), styrene (35 µL, 0.3 mmol, 1.5 equiv), palladium (II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and silver carbonate (110 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 98:2 hexane/ethyl acetate) afforded the desired product as a white solid (36 mg, 66%), mp 132-134 ºC. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.53 (d, $J$ = 7.5 Hz, 2H), 7.31-7.47 (m, 4H), 6.98 (d, $J$ = 16.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): $\delta$ 144.8 (dm, $J$ = 248.8 Hz), 139.7 (dm, $J$ = 252.8 Hz), 137.7 (dm, $J$ = 248.2 Hz), 137.1 (td, $J$ = 8.2 Hz, 2.6 Hz), 136.4, 128.9, 128.8, 126.8 112.6 (d, $J$ = 2.4 Hz), 112.4 (td, $J$ = 13.6 Hz, 4.2 Hz); $^{19}$F NMR (470 MHz, $CDCl_3$): $\delta$ -146.0 (dd, $J$ = 21.6 Hz, 7.0 Hz, 2F), -159.8 (t, $J$ = 20.7 Hz, 1F), -166.2 (td, $J$ = 20.7 Hz, 7.0 Hz, 2F); IR (neat): $\upsilon_{max}$ 1523, 1493, 1000, 959, 754 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{14}H_7F_5$ $[M]^+$: 270.0468; found: 270.0448.

**1-(4-Fluorostyryl)-2,3,4,5,6-pentafluorobenzene, 17b, Scheme 9**.[32] The same general procedure was followed by using pentafluorobenzoic acid (42.5 mg, 0.2 mmol, 1.0 equiv), 4-fluorostyrene (36 µL, 0.3 mmol, 1.5 equiv), palladium (II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and silver carbonate (110 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 98:2 hexane/ethyl acetate) afforded the desired product as a white solid (36 mg, 62%), mp 110-112 ºC. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 7.51 (dd, $J$ = 8.4 Hz, 5.4 Hz, 2H), 7.39 (d, $J$ = 16.8 Hz, 1H), 7.09 (t, $J$ = 8.4 Hz, 2H), 6.89 (d, $J$ = 16.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): $\delta$ 163.1 (d, $J$ = 248.0 Hz), 144.8 (dm, $J$ = 249.0 Hz), 139.7 (dm, $J$ = 253.5 Hz), 137.7 (dm, $J$ = 249.0 Hz), 135.9 (td, $J$ =

9.0 Hz, 1.5 Hz), 132.6 (d, *J* = 3.0 Hz), 128.5 (d, *J* = 7.5 Hz), 115.9 (d, *J* = 22.5 Hz), 112.4, 112.2 (td, *J* = 13.5 Hz, 4.5 Hz); $^{19}$F NMR (470 MHz, $CDCl_3$): $\delta$ -115.2 (s, 1F), -146.1 (dd, *J* = 21.2 Hz, 7.5 Hz, 2F), -159.6 (t, *J* = 20.7 Hz, 1F), -166.1 (td, *J* = 21.2 Hz, 7.5 Hz, 2F); IR (neat): $\upsilon_{max}$ 1519, 1492, 1240, 1003, 958 cm$^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{14}H_6F_6$ $[M]^+$: 288.0374; found: 288.0365.

**1-(4-Chlorostyryl)-2,3,4,5,6-pentafluorobenzene, 17c, Scheme 9**. The same general procedure was followed by using pentafluorobenzoic acid (42.5 mg, 0.2 mmol, 1.0 equiv), 4-chlorostyrene (38 µL, 0.3 mmol, 1.5 equiv), palladium (II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and silver carbonate (110 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 98:2 hexane/ethyl acetate) afforded the desired product as a white solid (44 mg, 73%), mp 98-100 ºC. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 7.47 (d, *J* = 8.4 Hz, 2H), 7.37-7.41 (m, 3H), 6.96 (d, *J* = 16.8 Hz, 1H); $^{13}$C{$^1$H} NMR (150 MHz, $CDCl_3$): $\delta$ 144.8 (dm, *J* = 249.2 Hz), 139.8 (dm, J = 253.5 Hz), 137.8 (dm, *J* = 249.2 Hz), 135.7 (td, *J* = 9.0 Hz, 3.0 Hz), 134.9, 134.7, 129.0, 128.0, 113.2 (d, J = 1.5 Hz), 112.0 (td, *J* = 13.5 Hz, 4.5 Hz); $^{19}$F NMR (470 MHz, $CDCl_3$): $\delta$ -142.6 (dd, *J* = 22.1 Hz, 7.0 Hz, 2F), -156.0 (t, *J* = 20.7 Hz, 1F), -162.8 (td, *J* = 20.7 Hz, 6.6 Hz, 2F) ; IR (neat): $\upsilon_{max}$ 1520, 1490, 1004, 958, 811 cm$^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{14}H_6ClF_5$ $[M]^+$: 304.0078; found: 304.0061.

**1-(4-Bromostyryl)-2,3,4,5,6-pentafluorobenzene, 17d, Scheme 9**. The same general procedure was followed by using pentafluorobenzoic acid (42.5 mg, 0.2 mmol, 1.0 equiv), 4-bromostyrene (39 µL, 0.3 mmol, 1.5 equiv), palladium (II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and silver carbonate (110 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 98:2 hexane/ethyl acetate) afforded the desired product as a white solid (47 mg, 67%), mp 99-101 ºC. $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ 7.52 (d, *J* = 8.1 Hz, 2H), 7.34-7.41 (m, 3H), 6.97 (d, *J* = 16.8 Hz, 1H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 75 MHz): $\delta$ 144.7 (dm, *J* = 248.9 Hz), 139.8 (dm, *J* = 252.8 Hz), 137.7 (dm, *J* = 249.8 Hz), 135.8 (td, *J* = 9.0 Hz, 1.5 Hz), 135.3, 132.0, 128.2, 122.9, 113.3 (d, *J* = 3.0 Hz), 112.0 (td, *J* = 13.5 Hz, 4.5 Hz); $^{19}$F NMR (470 MHz, $CDCl_3$): $\delta$ -142.6 (dd, *J* = 21.2 Hz, 6.6 Hz, 2F), -155.9 (t, *J* = 21.6 Hz, 1F), -162.7 (td, *J* = 21.6 Hz, 7.0 Hz, 2F); IR

(neat): $\upsilon_{max}$ 1519, 1492, 1002, 961, 810 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{14}H_6BrF_5$ $[M]^+$: 347.9573, 349.9553; found: 347.9570, 349.9529.

**1-(4-Methylstyryl)-2,3,4,5,6-pentafluorobenzene, 17e, Scheme 9**.[27a] The same general procedure was followed by using pentafluorobenzoic acid (42.5 mg, 0.2 mmol, 1.0 equiv), 4-methylstyrene (40 µL, 0.3 mmol, 1.5 equiv), palladium (II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and silver carbonate (110 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 97:3 hexane/ethyl acetate) afforded the desired product as a white solid (41 mg, 73%), mp 142-144 ºC. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.38-7.44 (m, 3H), 7.20 (d, *J* = 8.1 Hz, 2H), 6.93 (d, *J* = 16.8 Hz, 1H), 2.38 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): $\delta$ 144.7 (dm, *J* = 248.3 Hz), 139.5 (dm, *J* = 252.8 Hz), 139.1, 137.7 (dm, *J* = 250.5 Hz), 137.1 (td, *J* = 8.2 Hz, 2.2 Hz), 133.7, 129.5, 126.8, 112.6 (td, *J* = 13.5 Hz, 4.5 Hz), 111.6 (d, *J* = 2.2 Hz), 21.3; $^{19}F$ NMR (470 MHz, $CDCl_3$): -143.0 (dd, *J* = 22.6 Hz, 6.1 Hz, 2F), -157.1 (t, *J* = 20.7 Hz, 1F), -163.2 (td, *J* = 20.7 Hz, 6.1 Hz, 2F); IR (neat): $\upsilon_{max}$ 2924, 1519, 1492, 1001, 958, 804 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{15}H_9F_5$ $[M]^+$: 284.0624; found: 284.0615.

**1-(4-Ethylstyryl)-2,3,4,5,6-pentafluorobenzene, 17f, Scheme 9**. The same general procedure was followed by using pentafluorobenzoic acid (42.5 mg, 0.2 mmol, 1.0 equiv), 4-ethylstyrene (44 µL, 0.3 mmol, 1.5 equiv), palladium (II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and silver carbonate (110 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 97:3 hexane/ethyl acetate) afforded the desired product as a white solid (33 mg, 56%), mp 134-136 ºC. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.39-7.47 (m, 3H), 7.32 (d, *J* = 8.1 Hz, 2H), 6.94 (d, *J* = 16.5 Hz, 1H), 2.67 (q, *J* = 7.5 Hz, 2H), 1.26 (t, *J* = 7.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, CDCl3): $\delta$ 144.7 (dm, *J* = 248.4 Hz), 145.5, 139.5 (dm, *J* = 252.0 Hz), 137.8 (dm, *J* = 249.2 Hz), 137.1 (t, *J* = 8.2 Hz), 134.0, 128.4, 126.9, 112.6 (td, *J* = 13.5 Hz, 3.8 Hz), 111.7 (d, *J* = 1.5 Hz), 28.7, 15.4; $^{19}F$ NMR (470 MHz, $CDCl_3$): $\delta$ -143.0 (dd, *J* = 20.2 Hz, 5.2 Hz, 2F), -157.1 (t, *J* = 20.7 Hz, 1F), -163.2 (td, *J* = 20.7 Hz, 5.6 Hz, 2F); IR (neat): $\upsilon_{max}$ 2925, 1522, 1491, 1001, 959, 819 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{16}H_{11}F_5$ $[M]^+$: 298.0781; found: 298.0784.

**1-(4-*tert*-Butylstyryl)-2,3,4,5,6-pentafluorobenzene, 17g, Scheme 9**. The same general procedure was followed by using pentafluorobenzoic acid (51 mg, 0.24 mmol, 1.2 equiv),

4-*tert*-butylstyrene (37 µL, 0.2 mmol, 1.0 equiv), palladium (II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and silver carbonate (110 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 98:2 hexane/ethyl acetate) afforded the desired product as a white solid (46 mg, 70%), mp 100-102 ºC. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.35-7.49 (m, 5H), 6.94 (d, $J$ = 16.8 Hz, 1H), 1.34 (s, 9H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): $\delta$ 152.4, 144.7 (dm, $J$ = 248.2 Hz), 139.5 (dm, $J$ = 252.0 Hz), 137.8 (dm, $J$ = 249.0 Hz), 137.0 (t, $J$ = 8.2 Hz), 133.7, 126.6, 125.8, 122.6 (td, $J$ = 13.5 Hz, 3.8 Hz), 111.8, 34.8, 31.2; $^{19}$F NMR (470 MHz, $CDCl_3$): -142.9 (dd, $J$ = 21.6 Hz, 6.6 Hz, 2F), -157.0 (t, $J$ = 20.7 Hz, 1F), -163.2 (td, $J$ = 21.2 Hz, 6.6 Hz, 2F); IR (neat): $\upsilon_{max}$ 2971, 1520, 1498, 1003, 960, 822 cm$^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{18}H_{15}F_5$ $[M]^+$: 326.1094; found: 326.1081.

**1-(4-Methoxystyryl)-2,3,4,5,6-pentafluorobenzene, 17h, Scheme 9**.[32] The same general procedure was followed by using pentafluorobenzoic acid (51 mg, 0.24 mmol, 1.2 equiv), 4-vinylanisole (27 µL, 0.2 mmol, 1.0 equiv), palladium (II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and silver carbonate (110 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 97:3 hexane/ethyl acetate) afforded the desired product as a white solid (43 mg, 72%), mp 128-130 ºC. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 7.47 (d, $J$ = 9.0 Hz, 2H), 7.38 (d, $J$ = 16.8 Hz, 1H), 6.92 (d, $J$ = 9.0, 2H), 6.83 (d, $J$ = 16.8 Hz, 1H), 3.85 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): $\delta$ 160.3, 144.6 (dm, $J$ = 247.5 Hz), 139.3 (dm, $J$ = 252.0 Hz), 137.8 (dm, $J$ = 247.5 Hz), 136.6 (td, $J$ = 9.0 Hz, 1.5 Hz), 129.2, 128.2, 114.2, 112.7 (td, $J$ = 13.5 Hz, 4.5 Hz), 110.3 (d, $J$ = 3.0 Hz), 55.3; $^{19}$F NMR (470 MHz, $CDCl_3$): $\delta$ -143.2 (dd, $J$ = 21.2 Hz, 5.2 Hz, 2F), -157.5 (t, $J$ = 20.7 Hz, 1F), -163.3 (td, $J$ = 20.7 Hz, 5.6 Hz, 2F); IR (neat): $\upsilon_{max}$ 2926, 1603, 1519, 1492, 1255, 1001, 956, 816 cm$^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{15}H_9OF_5$ $[M]^+$: 300.0574; found: 300.0561.

**4-(Perfluorostyryl)phenyl acetate, 17i, Scheme 9**. The same general procedure was followed by using pentafluorobenzoic acid (51 mg, 0.24 mmol, 1.2 equiv), 4-acetoxystyrene (30 µL, 0.2 mmol, 1.0 equiv), palladium (II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and silver carbonate (110 mg, 0.4 mmol, 2.0 equiv). In this case little bit unreacted styrene was there with the same polarity desired products. To purify the desired products high pressure vacuum pump was used to remove the unreacted styrene.

Column chromatography ($SiO_2$, eluting with 97:3 hexane/ethyl acetate) afforded the desired product as a white solid (38 mg, 58%), mp 130-132 ºC. $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 7.54 (d, $J$ = 8.4 Hz, 2H), 7.41, (d, $J$ = 16.8 Hz, 1H), 7.13 (d, $J$ = 8.4 Hz, 2H), 6.93 (d, $J$ = 16.8 Hz, 1H), 2.3 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): $\delta$ 169.3, 151.0, 144.8 (dm, $J$ = 249.0 Hz), 139.7 (dm, $J$ = 252.0 Hz), 137.7 (dm, $J$ = 250.5 Hz), 136.0 (td, $J$ = 9.0 Hz, 3.0 Hz), 134.2, 127.9, 122.0, 112.8 (d, $J$ = 1.5 Hz), 112.2 (td, $J$ = 13.5 Hz, 3.0 Hz), 21.1; $^{19}F$ NMR (470 MHz, $CDCl_3$): $\delta$ -142.7 (dd, $J$ = 21.6 Hz, 6.1 Hz, 2F), -156.4 (t, $J$ = 20.7 Hz, 1F), -162.9 (td, $J$ = 20.2 Hz, 5.6 Hz, 2F); IR (neat): $\upsilon_{max}$ 2925, 1761, 1518, 1497, 1197, 1007, 957 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{16}H_9O_2F_5$ $[M]^+$: 328.0523; found: 328.0525.

**(4-(Perfluorostyryl)phenoxy)(tert-butyl)dimethylsilane, 17j, Scheme 9**. The same general procedure was followed by using pentafluorobenzoic acid (51 mg, 0.24 mmol, 1.2 equiv), 4-(*tert*-butyldimethylsiloxy)styrene (47 µL, 0.2 mmol, 1.0 equiv), palladium (II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and silver carbonate (110 mg, 0.4 mmol, 2.0 equiv). Here little bit unreacted styrene was there with the same polarity desired products. To purify the desired products high pressure vacuum pump was used to remove the unreacted styrene. Column chromatography ($SiO_2$, eluting with 97:3 hexane/ethyl acetate) afforded the desired product as a white solid (54 mg, 68%), mp 116-118 ºC. $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 7.42 (d, $J$ = 8.4 Hz, 2H), 7.37 (d, $J$ = 16.8 Hz, 1H), 6.86 (d, $J$ = 9.0 Hz, 2H), 6.84 (d, $J$ = 16.8 Hz, 1H), 1.01 (s, 9H), 0.24 (s, 6H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): $\delta$ 156.6, 144.6 (dm, $J$ = 248.1 Hz), 139.3 (dm, $J$ = 252.0 Hz), 137.7 (dm, $J$ = 248.7 Hz), 136.8 (td, $J$ = 9.0 Hz, 1.5 Hz), 129.8, 128.2, 120.5, 112.7 (td, $J$ = 13.5 Hz, 4.5 Hz), 110.5 (d, $J$ = 1.5 Hz), 25.6, 18.2, -4.4; $^{19}F$ NMR (470 MHz, $CDCl_3$): $\delta$ -143.2 (dd, $J$ = 22.6 Hz, 6.1 Hz, 2F), -157.5 (t, $J$ = 20.7 Hz, 1F), -163.3 (td, $J$ = 20.7 Hz, 6.6 Hz, 2F); IR (neat): $\upsilon_{max}$ 2858, 1600, 1521, 1492, 1276, 1003, 960, 916 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{20}H_{21}OSiF_5$ $[M]^+$: 400.1282; found: 400.1278.

**1-(3-Fluorostyryl)-2,3,4,5,6-pentafluorobenzene, 17k, Scheme 9**. The same general procedure was followed by using pentafluorobenzoic acid (42.5 mg, 0.2 mmol, 1.0 equiv), 3-fluorostyrene (36 µL, 0.3 mmol, 1.5 equiv), palladium (II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and silver carbonate (110 mg, 0.4 mmol, 2.0 equiv). Column

chromatography ($SiO_2$, eluting with 98:2 hexane/ethyl acetate) afforded the desired product as a white solid (35 mg, 61%), mp 82-84 ºC. $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 7.39 (d, $J$ = 16.2 Hz, 1H), 7.34-7.37 (m, 1H), 7.29 (d, $J$ = 7.8 Hz, 1H), 7.22-7.24 (m, 1H), 7.04 (td, $J$ = 8.4 Hz, 1.8 Hz, 1H), 6.98 (d, $J$ = 16.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): $\delta$ 163.1 (d, $J$ = 246.0 Hz), 144.8 (dm, $J$ = 249.0 Hz), 139.9 (dm, $J$ = 253.5 Hz), 138.7 (d, $J$ = 7.5 Hz), 137.8 (dm, $J$ = 247.5 Hz), 135.8 (t, $J$ = 7.5 Hz), 130.3 (d, $J$ = 9.0 Hz), 122.8 (d, $J$ = 3.0 Hz), 115.8 (d, $J$ = 21.0 Hz), 114.0 (d, $J$ = 3.0 Hz), 113.2 (d, $J$ = 22.5 Hz), 111.9 (td, $J$ = 13.5 Hz, 3.0 Hz); $^{19}F$ NMR (470 MHz, $CDCl_3$): $\delta$ -112.8 (s, 1F), -142.4 (dd, $J$ = 20.7 Hz, 5.2 Hz, 2F), -155.7 (t, $J$ = 20.7 Hz, 1F), -162.7 (m, 2F); IR (neat): $\upsilon_{max}$ 1521, 1494, 1004, 955, 680 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{14}H_6F_6$ $[M]^+$: 288.0374; found: 288.0365.

**1-(3-Chlorostyryl)-2,3,4,5,6-pentafluorobenzene, 17l, Scheme 9**. The same general procedure was followed by using pentafluorobenzoic acid (42.5 mg, 0.2 mmol, 1.0 equiv), 3-chlorostyrene (38 µL, 0.3 mmol, 1.5 equiv), palladium (II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and silver carbonate (110 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 98:2 hexane/ethyl acetate) afforded the desired product as a white solid (43 mg, 71%), mp 74-76 ºC. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.51 (s, 1H), 7.31-7.42 (m, 4H), 6.98 (d, $J$ = 16.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): $\delta$ 144.9 (dm, $J$ = 246.8 Hz), 140.0 (dm, $J$ = 256.5 Hz), 138.3, 137.8 (dm, $J$ = 251.2 Hz), 135.6 (t, $J$ = 8.2 Hz), 134.9, 130.0, 128.8, 126.7, 125.1, 114.1, 111.9 (td, J = 13.5 Hz, 4.5 Hz); $^{19}F$ NMR (470 MHz, $CDCl_3$): $\delta$ -142.4 (dd, $J$ = 21.2 Hz, 5.6 Hz, 2F), -155.6 (t, $J$ = 20.7 Hz, 1F), 162.6 (td, $J$ = 21.6 Hz, 7.0 Hz, 2F); IR (neat): $\upsilon_{max}$ 1519, 1497, 1003, 964, 782 cm-1; HRMS (EI, *m/z*) calcd. for $C_{14}H_6ClF_5$ $[M]^+$: 304.0078; found: 304.0075.

**1-(3-Bromostyryl)-2,3,4,5,6-pentafluorobenzene, 17m, Scheme 9**. The same general procedure was followed by using pentafluorobenzoic acid (42.5 mg, 0.2 mmol, 1.0 equiv), 3-bromostyrene (39 µL, 0.3 mmol, 1.5 equiv), palladium (II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and silver carbonate (110 mg, 0.4 mmol, 2.0 equiv). Here little bit unreacted styrene was there with the same polarity desired products. To purify the desired products high pressure vacuum pump was used to remove the unreacted

styrene. Column chromatography ($SiO_2$, eluting with 98:2 hexane/ethyl acetate) afforded the desired product as a white solid (42 mg, 60%), mp 76-78 ºC. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.67-7.68 (m, 1H), 7.43-7.48 (m, 2H), 7.36 (d, *J* = 16.8 Hz, 1H), 7.24-7.29 (m, 1H), 6.97 (d, *J* = 16.8 Hz, 1H); $^{13}$C{$^1$H}NMR (75 MHz, $CDCl_3$): $\delta$ 144.9 (dm, *J* = 249.4 Hz), 140.0 (dm, *J* = 253.6 Hz), 138.6, 137.8 (dm, *J* = 250.5 Hz), 135.5 (t, *J* = 8.2 Hz), 131.8, 130.3, 129.6, 125.5, 123.0, 114.1, 111.9 (td, *J* = 13.5 Hz, 3.8 Hz); $^{19}$F NMR (470 MHz, $CDCl_3$): $\delta$ -145.6 (dd, *J* = 20.7 Hz, 7.0 Hz, 2F), -158.8 (t, *J* = 20.7 Hz, 1F), -165.9 (td, *J* = 20.7 Hz, 7.0 Hz, 2F); IR (neat): $\upsilon_{max}$ 1521, 1496, 1002, 964, 780 cm$^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{14}H_6BrF_5$ $[M]^+$: 347.9573, 349.9553; found: 347.9573, 349.9541.

**1-(3-Methylstyryl)-2,3,4,5,6-pentafluorobenzene, 17n, Scheme 9**. The same general procedure was followed by using pentafluorobenzoic acid (42.5 mg, 0.2 mmol, 1.0 equiv), 3-methylstyrene (32 µL, 0.3 mmol, 1.5 equiv), palladium (II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and silver carbonate (110 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 98:2 hexane/ethyl acetate) afforded the desired product as a white solid (37 mg, 65%), mp 104-106 ºC. $^1$H NMR (600 MHz $CDCl_3$): $\delta$ 7.40 (d, *J* = 16.8 Hz, 1H), 7.33-7.34 (m, 2H), 7.29 (t, *J* = 7.2 Hz, 1H), 7.16 (d, *J* = 7.2 Hz, 1H), 6.97 (d, *J* = 16.8 Hz, 1H), 2.40 (s, 3H); $^{13}$C{$^1$H} NMR (150 MHz, $CDCl_3$): $\delta$ 144.8 (dm, *J* = 249.0 Hz), 139.6 (dm, *J* = 253.5 Hz), 138.5, 137.7 (dm, *J* = 249.0 Hz), 137.3 (td, *J* = 9.0 Hz, 3.0 Hz), 136.4, 129.8, 128.7, 127.5, 124.0, 112.43 (td, *J* = 13.5 Hz, 3.0 Hz), 112.40 (d, *J* = 3.0 Hz), 21.4; $^{19}$F NMR (470 MHz, $CDCl_3$): $\delta$ -142.8 (dd, *J* = 21.6 Hz, 7.0 Hz, 2F), -156.8 (t, *J* = 20.7 Hz, 1F), -163.1 (m, 2F); IR (neat): $\upsilon_{max}$ 2924, 1521, 1493, 1000, 962, 783 cm$^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{15}H_9F_5$ $[M]^+$: 284.0624; found: 284.0598.

**1-(3-Methoxystyryl)-2,3,4,5,6-pentafluorobenzene, 17o, Scheme 9**. The same general procedure was followed by using pentafluorobenzoic acid (51 mg, 0.24 mmol, 1.2 equiv), 3-vinylanisole (28 µL, 0.2 mmol, 1.0 equiv), palladium (II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and silver carbonate (110 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 97:3 hexane/ethyl acetate) afforded the desired product as a white solid (45 mg, 75%), mp 140-142 ºC. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 7.40 (d, *J* = 16.8 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 1H), 7.13 (d, J = 7.8 Hz, 1H), 7.05 (d, *J* =

1.8 Hz, 1H), 6.97 (d, *J* = 16.8 Hz, 1H), 6.90 (dd, *J* = 7.8 Hz, 1.8 Hz, 1H), 3.86 (s, 3H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): $\delta$ 159.9, 144.8 (dm, *J* = 249.0 Hz), 139.7 (dm, *J* = 252.0 Hz), 137.8, 137.7 (dm, *J* = 247.5 Hz), 137.0 (td, *J* = 9.0 Hz, 3.0 Hz), 129.8, 119.5, 114.6, 113.0 (d, *J* = 3.0 Hz), 112.3 (td, *J* = 13.5 Hz, 3.0 Hz), 112.1, 55.3; $^{19}F$ NMR (470 MHz, $CDCl_3$): $\delta$ -142.7 (dd, *J* = 22.1 Hz, 6.1 Hz, 2F), -156.5 (t, *J* = 20.7 Hz, 1F), -163.0 (td, *J* = 21.2 Hz, 6.1 Hz, 2F); IR (neat): $\upsilon_{max}$ 1578, 1522, 1495, 1268, 1045, 1002, 965, 778 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{15}H_9OF_5$ $[M]^+$: 300.0574; found: 300.0564.

**1-(3-(Trifluoromethyl)styryl)-2,3,4,5,6-pentafluorobenzene, 17p, Scheme 9**. The same general procedure was followed by using pentafluorobenzoic acid (42.5 mg, 0.2 mmol, 1.0 equiv), 3-trifluoromethylstyrene (45 µL, 0.3 mmol, 1.5 equiv), palladium (II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and silver carbonate (110 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 98:2 hexane/ethyl acetate) afforded the desired product as a white solid (45 mg, 67%), mp 76-78 ºC. $^{1}H$ NMR (600 MHz, $CDCl_3$): $\delta$ 7.76 (s, 1H), 7.71 (d, *J* = 7.8 Hz, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 1H), 7.46 (d, *J* = 16.2 Hz, 1H), 7.05 (d, *J* = 16.8 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): $\delta$ 144.9 (dm, *J* = 249.0 Hz), 140.1 (dm, *J* = 255.0 Hz), 137.2, 137.8 (dm, *J* = 251.7 Hz), 135.5 (td, *J* = 9.0 Hz, 1.5 Hz), 131.4 (q, *J* = 33.0 Hz), 129.8, 129.3, 123.9 (q, *J* = 271.5 Hz), 125.4 (q, *J* = 4.5 Hz), 123.6 (q, *J* = 3.0 Hz), 114.6 (d, *J* = 3.0 Hz), 111.7 (td, *J* = 13.5 Hz, 4.5 Hz); $^{19}F$ NMR (470 MHz, $CDCl_3$): $\delta$ -66.1 (s, 1F), -145.6 (dd, *J* = 21.2 Hz, 7.5 Hz, 2F), -158.6 (t, *J* = 20.7 Hz, 1F), -165.8 (td, *J* = 21.2 Hz, 7.5 Hz, 2F); IR (neat): $\upsilon_{max}$ 2924, 1520, 1497, 1331, 1128, 1004, 961, 695 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{15}H_6F_8$ $[M]^+$: 338.0342; found: 338.0343.

**1-(2-Methylstyryl)-2,3,4,5,6-pentafluorobenzene, 17q, Scheme 9**. The same general procedure was followed by using pentafluorobenzoic acid (42.5 mg, 0.2 mmol, 1.0 equiv), 2-methylstyrene (31 µL, 0.3 mmol, 1.5 equiv), palladium (II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and silver carbonate (110 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 98:2 hexane/ethyl acetate) afforded the desired product as a white solid (34 mg, 60%), mp 112-114 ºC. $^{1}H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.68 (d, *J* = 16.8 Hz, 1H), 7.57-7.61 (m, 1H), 7.19-7.28 (m, 3H), 6.86 (d, *J* = 16.5 Hz, 1H), 2.42 (s, 3H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$): $\delta$ 144.8 (dm, *J* = 248.2 Hz), 139.7

(dm, *J* = 252.8 Hz), 137.8 (dm, *J* = 249.8 Hz), 136.4, 135.7, 135.2 (td, *J* = 8.2 Hz, 3.0 Hz), 130.6, 128.8, 126.4, 125.3, 113.8 (d, *J* = 3.0 Hz), 112.6 (td, *J* = 13.5 Hz, 4.5 Hz), 19.7; $^{19}$F NMR (470 MHz, $CDCl_3$): $\delta$ -143.0 (dd, *J* = 20.2 Hz, 7.5 Hz, 2F), -156.7 (t, *J* = 20.7 Hz, 1F), -163.0 (td, *J* = 21.2 Hz, 7.0 Hz, 2F); IR (neat): $\upsilon_{max}$ 2924, 1522, 1494, 1000, 962, 754 cm$^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{15}H_9F_5$ $[M]^+$: 284.0624; found: 284.0620.

**1,3-Dimethoxy-5-(perfluorostyryl)benzene, 17r, Scheme 9**. The same general procedure was followed by using pentafluorobenzoic acid (51 mg, 0.24 mmol, 1.2 equiv), 3,5-dimethoxystyrene (33 µL, 0.2 mmol, 1.0 equiv), palladium (II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and silver carbonate (110 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 97:3 hexane/ethyl acetate) afforded the desired product as a white solid (46 mg, 69%), mp 103-105 ºC. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.36 (d, *J* = 16.5 Hz, 1H), 6.95 (d, *J* = 16.8 Hz, 1H), 6.67 (d, *J* = 2.1 Hz, 2H), 6.46 (t, *J* = 2.1 Hz, 1H), 3.84 (s, 6H); $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$): $\delta$ 161.1, 144.8 (dm, *J* = 249.2 Hz), 139.7 (dm, *J* = 253.0 Hz), 137.7 (dm, *J* = 249.8 Hz), 138.4, 137.1 (td, *J* = 8.2 Hz, 1.5 Hz), 113.1 (d, *J* = 2.2 Hz), 112.2 (td, *J* = 13.5 Hz, 4.5 Hz), 104.9, 101.1, 55.4; $^{19}$F NMR (470 MHz, $CDCl_3$): $\delta$ -142.6 (dd, *J* = 20.7 Hz, 5.6 Hz, 2F), -156.4 (t, *J* = 20.7 Hz, 1F), -163.0 (m, 2F); IR (neat): $\upsilon_{max}$ 1593, 1522, 1494, 1296, 1155, 1061, 1005 cm$^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{16}H_{11}O_2F_5$ $[M]^+$: 330.0679; found: 330.0678.

**1-(3,4-Dimethoxystyryl)-2,3,4,5,6-pentafluorobenzene, 17s, Scheme 9**. The same general procedure was followed by using pentafluorobenzoic acid (51 mg, 0.24 mmol, 1.2 equiv), 3,4-dimethoxystyrene (30 µL, 0.2 mmol, 1.0 equiv), palladium (II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and silver carbonate (110 mg, 0.4 mmol, 2.0 equiv). Here little bit unreacted styrene was there with the same polarity desired products. To purify the desired products high pressure vacuum pump was used to remove the unreacted styrene. Column chromatography ($SiO_2$, eluting with 97:3 hexane/ethyl acetate) afforded the desired product as a white solid (45 mg, 68%), mp 131-133 ºC. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 7.36 (d, *J* = 16.2 Hz, 1H), 7.08 (dd, *J* = 8.4 Hz, 2.4 Hz, 1H), 7.04 (d, *J* = 1.8 Hz, 1H), 6.87 (d, *J* = 7.8 Hz, 1H), 6.82 (d, *J* = 16.8 Hz, 1H), 3.95 (s, 3H), 3.92 (s, 3H); $^{13}$C{$^1$H} NMR (150 MHz, $CDCl_3$): $\delta$ 149.6, 149.2, 144.6 (dm, *J* = 247.5

Hz), 139.4 (dm, *J* = 247.5 Hz), 137.7 (dm, *J* = 247.5 Hz), 136.9 (td, *J* = 9.0 Hz, 1.5 Hz), 120.6, 112.6 (td, *J* = 13.5 Hz, 4.5 Hz), 111.1, 110.5 (d, *J* = 3.0 Hz), 108.8, 55.92, 55.90; $^{19}$F NMR (470 MHz, $CDCl_3$): $\delta$ -143.2 (dd, *J* = 20.7 Hz, 5.2 Hz, 2F), -157.3 (t, *J* = 20.7 Hz, 1F), -163.2 (td, *J* = 20.7 Hz, 5.2 Hz, 2F); IR (neat): $\upsilon_{max}$ 1520, 1494, 1262, 1022, 961 cm$^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{16}H_{11}O_2F_5Na$ $[M + Na]^+$: 353.0577; found: 353.0577.

**2-Methoxy-4-(perfluorostyryl)phenyl acetate, 17t, Scheme 9**. The same general procedure was followed by using pentafluorobenzoic acid (51 mg, 0.24 mmol, 1.2 equiv), 4-acetoxy-3-methoxystyrene (38 µL, 0.2 mmol, 1.0 equiv), palladium (II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and silver carbonate (110 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 97:3 hexane/ethyl acetate) afforded the desired product as a white solid (44 mg, 62%), mp 149-151 ºC. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 7.40 (d, *J* = 16.8 Hz, 1H), 7.12 (dd, *J* = 8.4 Hz, 1.8 Hz, 1H), 7.09 (s, 1H), 7.06 (d, *J* = 7.8 Hz, 1H), 6.91 (d, *J* = 16.8 Hz, 1H), 3.90 (s, 3H), 2.53 (s, 3H); $^{13}$C{$^1$H} NMR (150 MHz, $CDCl_3$): $\delta$ 168.9, 151.3, 144.8 (dm, *J* = 249.0 Hz), 140.3, 139.7 (dm, *J* = 252.6 Hz), 137.7 (dm, *J* = 250.5 Hz), 136.4 (td, *J* = 9.0 Hz, 1.5 Hz), 135.4, 123.1, 119.6, 112.9 (d, *J* = 1.5 Hz), 112.2 (td, *J* = 13.5 Hz, 3.0 Hz), 110.4, 55.9, 20.6; $^{19}$F NMR (470 MHz, $CDCl_3$): $\delta$ -142.7 (dd, *J* = 20.7 Hz, 5.6 Hz, 2F), -156.3 (t, *J* = 20.7 Hz, 1F), -162.9 (m, 2F); IR (neat): $\upsilon_{max}$ 1764, 1517, 1496, 1204, 1004, 968 cm$^{-1}$; HRMS (ESI, *m/z*) calcd. for C17H11O3F5Na $[M + Na]^+$: 381.0526; found: 381.0534.

**1,2,3,4-Tetrafluoro-5-styrylbenzene, 17u, Scheme 9**.[27a] The same general procedure was followed by using tetrafluorobenzoic acid (39 mg, 0.2 mmol, 1.0 equiv), styrene (35 µL, 0.3 mmol, 1.5 equiv), palladium (II) trifluoroacetate (13.4 mg, 0.04 mmol, 0.2 equiv), and silver carbonate (165 mg, 0.6 mmol, 3.0 equiv). 5% DMSO was used as a co solvent and the reaction was run for 4 hours at 120 $^o$C. Column chromatography ($SiO_2$, eluting with 98:2 hexane/ethyl acetate) afforded the desired product as a white solid (30 mg, 60%), mp 86-88 ºC. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 7.52 (d, *J* = 7.8 Hz, 2H), 7.39 (t, *J* = 7.8 Hz, 2H), 7.33 (t, *J* = 7.8 Hz, 1H), 7.18-7.22 (m, 1H), 7.08 -7.15 (m, 2H); $^{13}$C{$^1$H} NMR (150 MHz, $CDCl_3$): $\delta$ 147.3 (dm, *J* = 244.8 Hz), 145.3 (dm, *J* = 248.4 Hz), 141.0 (dm, *J* = 250.0 Hz), 139.6 (dm, *J* = 252.9 Hz), 136.1, 132.9 (t, *J* = 3.0 Hz), 128.8, 128.7, 126.8, 121.7 (m), 117.9 (t, *J* = 3.0 Hz), 107.4 (dt, *J* = 21.0 Hz, 3.0 Hz); $^{19}$F NMR (470

MHz, $CDCl_3$): $\delta$ -139.8 (dd, $J$ = 21.2 Hz, 11.3 Hz, 1F), -144.1 (dd, $J$ = 20.7 Hz, 10.8 Hz, 1F) -156.0 (t, $J$ = 19.3 Hz, 1F), -157.0 (t, $J$ = 20.7 Hz, 1F); IR (neat): $\upsilon_{max}$ 1527, 1477, 1039, 942, 756, 693 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{14}H_8F_4$ $[M]^+$: 252.0562; found: 252.0556.

**1-(2,6-Difluorostyryl)benzene, 17v, Scheme 9**.[27a] The same general procedure was followed by using difluorobenzoic acid (32 mg, 0.2 mmol, 1.0 equiv), styrene (35 µL, 0.3 mmol, 1.5 equiv), palladium (II) trifluoroacetate (13.4 mg, 0.04 mmol, 0.2 equiv), and silver carbonate (165 mg, 0.4 mmol, 3.0 equiv). 5% DMSO was used as a co solvent and the reaction was run for 4 hours at 120 $^oC$. Column chromatography ($SiO_2$, eluting with 98:2 hexane/ethyl acetate) afforded the desired product as a white solid (30 mg, 70%), mp 65-67 ºC. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.54 (d, $J$ = 7.2 Hz, 2H), 7.25-7.42 (m, 4H), 7.11-7.18 (m, 2H), 6.91 (t, $J$ = 8.4 Hz, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): $\delta$ 161.0 (dm, $J$ = 249.8 Hz), 137.4, 135.1 (t, $J$ = 8.1 Hz), 128.7, 128.2, 127.8 (t, $J$ = 10.5 Hz), 126.7, 115.2, 114.8 (t, $J$ = 15.0 Hz), 111.5 (m); $^{19}F$ NMR (470 MHz, $CDCl_3$): $\delta$ -113.0 (s, 2F); IR (neat): $\upsilon_{max}$ 1565, 1463, 1210, 993, 748 $cm^{-1}$.

**1-Cinnamyl-2,3,4,5,6-pentafluorobenzene, 17w, Scheme 9**.[41] The same general procedure was followed by using pentafluorobenzoic acid (42.5 mg, 0.2 mmol, 1.0 equiv), allylbenzene (40 µL, 0.3 mmol, 1.5 equiv), palladium (II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and silver carbonate (110 mg, 0.4 mmol, 2.0 equiv) except the reaction was run at 120 $^oC$. Column chromatography ($SiO_2$, eluting with 98:2 hexane/ethyl acetate) afforded the desired product as a colorless liquid (42 mg, 74%). $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 7.23-7.36 (m, 5H), 6.50 (d, $J$ = 15.6 Hz, 1H), 6.21-6.26 (m, 1H), 3.62 (dd, $J$ = 6.6 Hz, 0.6 Hz, 2H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): $\delta$ 145.0 (dm, $J$ = 244.5 Hz), 139.8 (dm, $J$ = 250.5 Hz), 137.5 (dm, $J$ = 249.0 Hz), 136.5, 132.4, 128.6, 127.6, 126.2, 124.2, 113.2 (td, $J$ = 19.5 Hz, 4.5 Hz), 25.6; $^{19}F$ NMR (470 MHz, $CDCl_3$): $\delta$ -143.9 (dd, $J$ = 21.6 Hz, 7.0 Hz, 2F), -157.3 (t, $J$ = 20.7 Hz, 1F), -162.5 (td, $J$ = 20.7 Hz, 7.0 Hz, 2F); IR (neat): $\upsilon_{max}$ 1498, 1118, 990, 963, 911, 754, 694 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{15}H_9F_5$ $[M]^+$: 284.0624; found: 284.0608.

**Gram scale reaction: (Synthesis of 1,2,3,4,5-Pentafluoro-6-styrylbenzene, Scheme 9, 17a).**

To an oven-dried 250 mL round bottom flask, a mixture of pentafluorobenzoic acid (1.0 g, 4.7 mmol, 1.0 equiv), palladium (II) trifluoroacetate (156 mg, 0.47 mmol, 0.1 equiv), and silver carbonate (2.6 g, 9.4 mmol, 2.0 equiv) was taken then dry DMF (80 mL) was added to it under nitrogen atmosphere. To this reaction mixture styrene (0.8 ml, 7.05 mmol,) was added via syringe. The reaction mixture was allowed to stir for 16 h at room temperature under nitrogen atmosphere. After completion (as detected by TLC), the reaction mixture was poured into water (60 mL) and extracted with ethyl acetate (80 mL). The organic layer was washed with water (30 mL) and brine (20 mL), dried over anhydrous $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The pure 1,2,3,4,5-pentafluoro-6-styrylbenzene (**17a**) was obtained as a white solid in 61% (775 mg) yield after column chromatography of the crude reaction mixture using ethyl acetate/hexane (98:2) as eluent.

**Experimental procedure for the preparation of 1-(2,3,5,6-Tetrafluoro-4-styrylphenyl)-1*H*-indole, 21a, Scheme 12 from 1,2,3,4,5-Pentafluoro-6-styrylbenzene(17a).**

Sodium *tert*-butoxide (53 mg, 0.55 mmol, 1.1 equiv) was added to a glass vial containing indole (59 mg, 0.5 mmol, 1.0 equiv) in dry DMA (3.0 mL). The mixture was stirred at room temperature for 1.0 min. The mixture was cooled and added to a cooled solution of 1,2,3,4,5-pentafluoro-6-styrylbenzene (162 mg, 0.6 mmol,1.2 equiv) in dry DMA (3.0 mL) under stirring in a 10 mL round bottom flask. After 15 min the cooling bath was removed and the reaction mixture was allowed to stir for 1 h at room temperature under nitrogen atmosphere. After completion (as detected by TLC), the reaction mixture was mixed with sat. $NH_4Cl$ (aq.) (5.0 mL) and water (10 mL) then extracted with ethyl acetate (20 mL) The organic layer was washed with water (10 mL) and brine (10 mL), dried over anhydrous $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography eluting with hexane/ethyl acetate (8:2) afforded the desired product as a white solid (156 mg, 85%), mp 130-132 ºC. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 7.75 (d, $J$ = 7.8 Hz, 1H), 7.61-7.64 (m, 3H), 7.46 (t, $J$ = 7.8 Hz, 2H), 7.40 (t, $J$ = 7.2 Hz, 1H), 7.33 (td, $J$ = 8.4 Hz, 1.2 Hz, 1H), 7.28 (td, $J$ = 7.8 Hz, 1.2 Hz, 1H), 7.23-7.26 (m, 2H), 7.18 (d, $J$ = 16.8 Hz, 1H), 6.83 (d, $J$ = 3.6 Hz, 1H); $^{13}$C{$^1$H}

NMR (150 MHz, $CDCl_3$): $\delta$ 145.0 (dm, $J$ = 249.2 Hz), 142.8 (dm, $J$ = 250.0 Hz), 138.0 (t, $J$ = 9.0 Hz), 136.4, 136.3, 129.2, 128.9, 128.7, 128.3, 127.1, 123.1, 121.2 (d, $J$ = 3.0 Hz), 116.6 (m), 116.2 (t, $J$ = 13.5 Hz), 113.2, 110.6, 105.5; $^{19}F$ NMR (470 MHz, $CDCl_3$): $\delta$ -145.6 (m, 2F), -150.7 (m, 2F); IR (neat): $\upsilon_{max}$ 1519, 1487, 1204, 971, 748, 693 $cm^{-1}$; HRMS (FAB, *m/z*) calcd. for $C_{22}H_{14}NF_4$ $[M + H]^+$: 368.1062; found: 368.1062.

**Experimental procedure for the preparation of 1-(2,3,5,6-Tetra(1*H*-pyrazol-1-yl)-4-styrylphenyl)-1*H*-indole, 23a, Scheme 12 from 1-(2,3,5,6-Tetrafluoro-4-styrylphenyl)-1*H*-indole(21a).**

Sodium *tert*-butoxide (48 mg, 0.5 mmol, 5.0 equiv) was added to a glass vial containing pyrazole (34 mg, 0.5 mmol, 5.0 equiv) in dry DMA (1.0 mL). The mixture was stirred at room temperature for 1.0 min. The mixture was cooled and added to a cooled solution of 1-(2,3,5,6-tetrafluoro-4-styrylphenyl)-1*H*-indole (37 mg, 0.1 mmol, 1.0 equiv) in dry DMA (1.0 mL) under stirring in a 10 mL round bottom flask. After 15 min the cooling bath was removed and the reaction mixture was allowed to stir for 1 h at room temperature under nitrogen atmosphere. After completion (as detected by TLC), the reaction mixture was quenched with sat. $NH_4Cl$ (aq.) (1.0 mL) then extracted with ethylacetate (20 mL) and water (10 mL). The organic layer was washed with water (10 mL) and brine (10 mL), dried over anhydrous $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography eluting with hexane/ethyl acetate (7:3) afforded the desired product as a white solid (55 mg, 98%), mp 280-282 ºC. $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 7.66 (d, $J$ = 1.8 Hz, 2H), 7.53 (d, $J$ = 2.4 Hz, 2H), 7.42-7.43 (m, 1H), 7.27-7.28 (m, 2H), 7.23-7.24 (m, 3H), 7.00-7.05 (m, 7H), 6.84 (d, $J$ = 3.0 Hz, 1H), 6.41 (d, $J$ = 3.0 Hz, 1H), 6.38 (d, $J$ = 16.8 Hz, 1H), 6.35 (t, $J$ = 1.8 Hz, 2H), 5.90 (t, $J$ = 1.8 Hz, 2H), 5.86 (d, $J$ = 16.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): $\delta$ 141.12, 141.10, 138.4, 137.17, 137.16, 136.9, 136.33, 136.28, 132.7, 132.5, 131.3, 128.8, 128.6, 128.3, 127.9, 126.8, 122.4, 120.5, 117.7, 109.6, 107.2, 106.8, 104.8; IR (neat): $\upsilon_{max}$ 2923, 1519, 1480, 1389, 1037, 950, 756 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{34}H_{25}N_9$ $[M]^+$: 559.2233; found: 559.2235.

**Experimental procedure for the preparation of Benzyl(2,3,5,6-tetrafluoro-4-styrylphenyl)sulfane, 25a, Scheme 12 from 1,2,3,4,5-Pentafluoro-6-styrylbenzene(17a).**

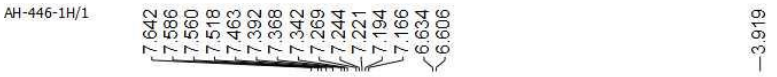
A mixture of 1,2,3,4,5-pentafluoro-6-styrylbenzene (27 mg, 0.1 mmol, 1.0 equiv.), phenylmethanethiol (14 µL, 0.12 mmol, 1.2 equiv) and TRIS (145 mg, 1.2 mmol, 12 equiv) in dry DMF (2.0 mL) was stirred for 12 h at room temperature under argon atmosphere in a 10 mL round bottom flask. After completion (as detected by TLC), the reaction mixture was poured into water (10 mL) and extracted with ethyl acetate (20 mL). The organic layer was washed with water (10 mL) and brine (10 mL), dried over anhydrous $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography eluting with hexane/ethyl acetate (8:2) to afford the desired product as a white solid (34 mg, 90%), mp 108-110 ºC. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 7.56 (d, $J$ = 7.8 Hz, 2H), 7.50 (d, $J$ = 16.8 Hz, 1H), 7.42 (t, $J$ = 7.2 Hz, 2H), 7.36 (t, $J$ = 7.8 Hz, 1H), 7.25-7.31 (m, 5H), 7.06 (d, $J$ = 16.8 Hz, 1H), 4.16 (s, 2H); $^{13}$C{$^1$H} NMR (150 MHz, $CDCl_3$): $\delta$ 147.1 (dm, $J$ = 242.8 Hz), 144.4 (dm, $J$ = 250.2 Hz), 137.6 (t, $J$ = 9.0 Hz), 136.5 (d, $J$ = 1.5 Hz), 129.0, 128.83, 128.78, 128.6, 127.7, 127.0, 117.0 (t, $J$ = 13.5 Hz), 113.7, 111.4 (t, $J$ = 21.0 Hz), 39.0 (t, $J$ = 3.0 Hz); $^{19}$F NMR (470 MHz, $CDCl_3$): $\delta$ -138.4 (dd, $J$ = 22.6 Hz, 11.3 Hz, 2F), -146.2 (dd, $J$ = 22.6 Hz, 11.3 Hz, 2F); IR (neat): $\upsilon_{max}$ 1468, 1064, 959, 752, 693 cm$^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{21}H_{14}SF_4$ $[M]^+$: 374.0752; found: 374.0734.

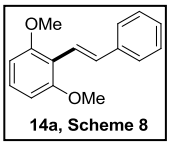
**Experimental procedure for the preparation of *tert*-Butyl (S)-1-(methoxycarbonyl)-2-(2,3,5,6-tetrafluoro-4-styrylphenylthio)ethylcarbamate, 27a, Scheme 12 from 1,2,3,4,5-Pentafluoro-6-styrylbenzene(17a).**

A mixture of 1,2,3,4,5-pentafluoro-6-styrylbenzene, **17a** (27 mg, 0.1 mmol, 1.0 equiv), *N*-(*tert*-butoxycarbonyl)-*L*-cysteine methyl ester (21 µL, 0.1 mmol, 1.0 equiv) and TRIS (25 mg, 0.2 mmol, 2.0 equiv) in dry DMF (2.0 mL) was stirred for 4.5 h at room temperature under argon atmosphere in a 10 mL round bottom flask. After completion (as detected by TLC), the reaction mixture was poured into water (10 mL) and extracted with ethyl acetate (20 mL). The organic layer was washed with water (10 mL) and brine (10 mL), dried over anhydrous $Na_2SO_4$ and the solvent was evaporated under reduced

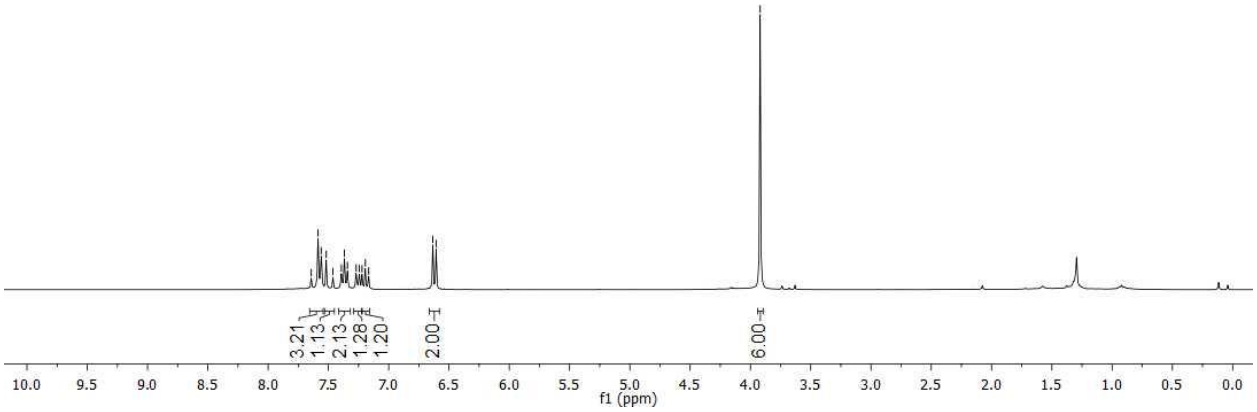
pressure. The crude product was purified by column chromatography eluting with hexane/ethyl acetate (7:3) to afford the desired product as a white solid (41 mg, 84%), mp 90-92 ºC. $^{1}$H NMR (600 MHz, $CDCl_3$): $\delta$ 7.56 (d, $J$ = 7.2 Hz, 2H), 7.52 (d, $J$ = 16.2 Hz, 1H), 7.42 (t, $J$ = 7.2 Hz, 2H), 7.36 (t, $J$ = 7.2 Hz, 1H), 7.08 (d, $J$ = 16.8 Hz, 1H), 5.39 (d, $J$ = 6.6 Hz, 1H), 4.58-4.60 (m, 1H), 3.70 (s, 3H), 3.47 (dd, $J$ = 14.4 Hz, 4.2 Hz, 1H), 3.38 (dd, $J$ = 14.4 Hz, 4.2 Hz, 1H), 1.41 (s, 9H); $^{13}$C{$^{1}$H} NMR (150 MHz, $CDCl_3$): $\delta$ 170.4, 154.7, 147.1(dm, $J$ = 243.0 Hz), 144.4 (dm, $J$ = 250.5 Hz), 138.0 (t, $J$ = 9.0 Hz), 136.4, 129.1, 128.8, 127.0, 117.5 (t, $J$ = 13.5 Hz), 113.5, 111.0 (t, $J$ = 21.0 Hz), 80.3, 53.7, 52.6, 36.6, 28.1; $^{19}$F NMR (470 MHz, $CDCl_3$): $\delta$ -134.5 (m, 2F), -142.6 (m, 2F); IR (neat): $\upsilon_{max}$ 1739, 1706, 1472, 1342, 1160, 1063, 1015, 963, 754 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{23}H_{23}NO_4SF_4$ $[M]^+$: 485.1284; found: 485.1287.

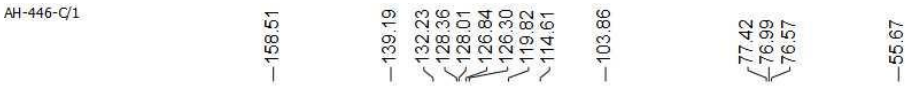
## III.9. $^{1}$H and $^{13}$C NMR spectra

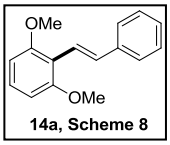


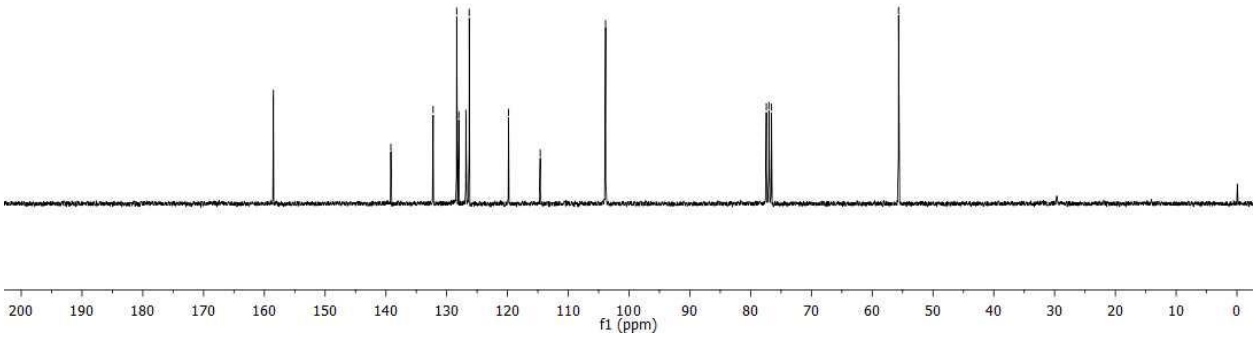

**14a, Scheme 8**

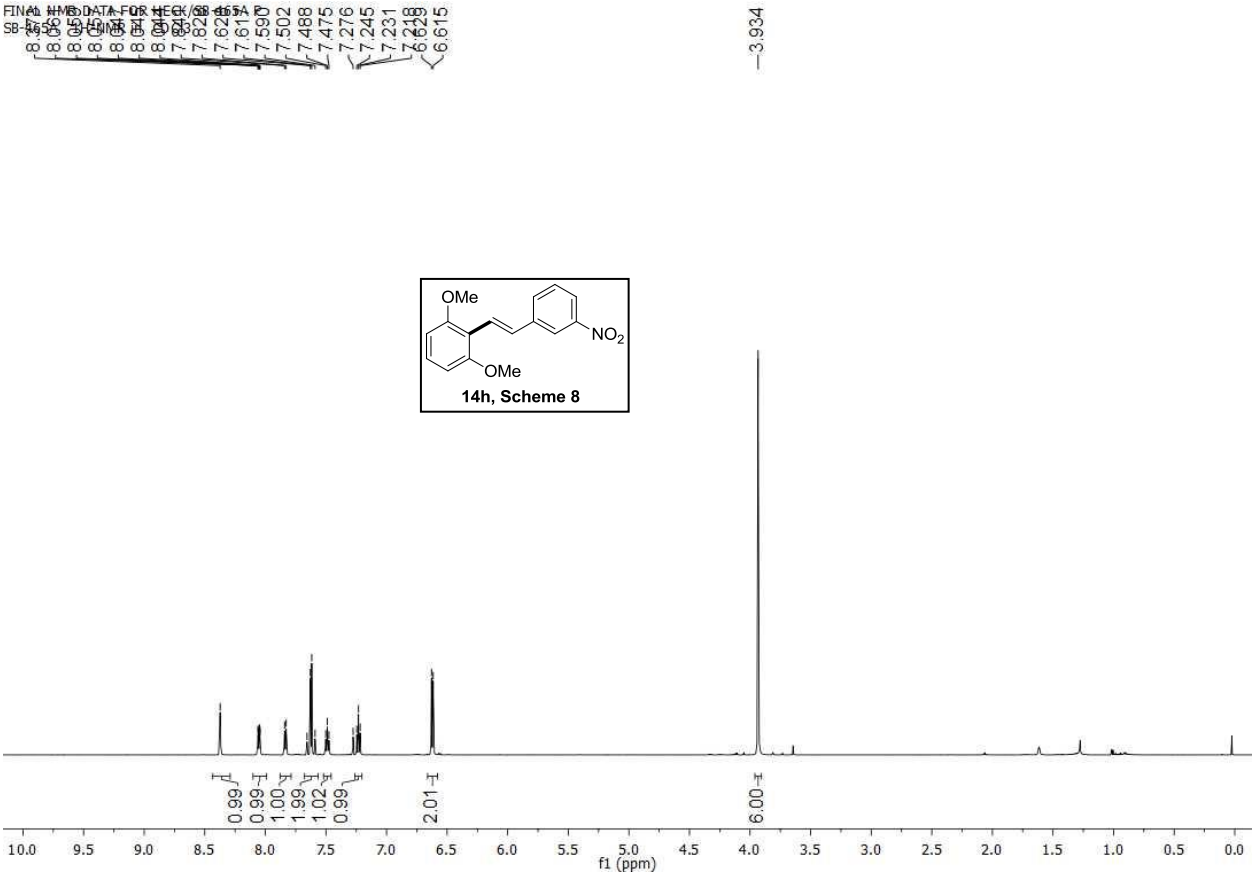


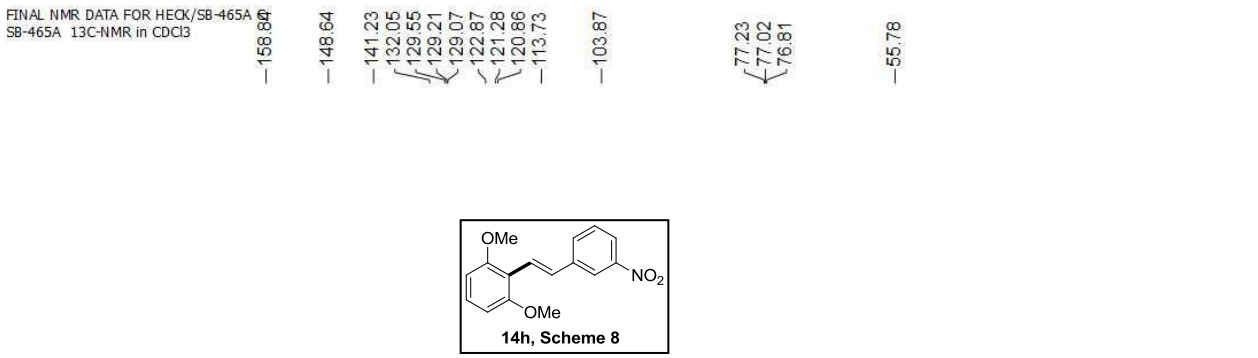



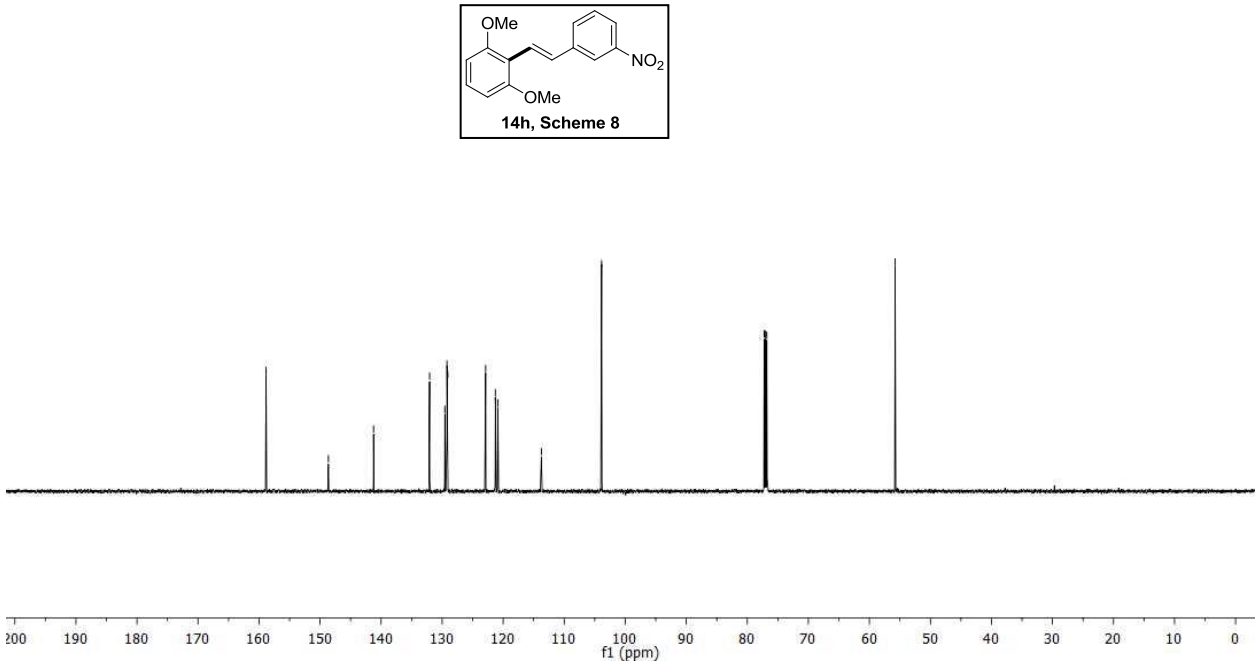




**14a, Scheme 8**



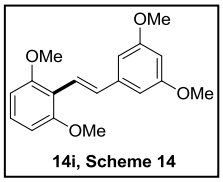

8.355
8.336
8.057
8.038
8.034
8.015
7.823
7.803
7.625
7.611
7.590
7.502
7.488
7.475
7.276
7.245
7.231
6.629
6.615
3.934
OMe
NO2
OMe
14h, Scheme 8
0.99
0.99
1.00
1.99
1.02
0.99
2.01
6.00
f1 (ppm)


FINAL NMR DATA FOR HECK/SB-465A
SB-465A 13C-NMR in CDCl3
158.84
148.64
141.23
132.05
129.55
129.21
129.07
122.87
121.28
120.86
113.73
103.87
77.23
77.02
76.81
55.78

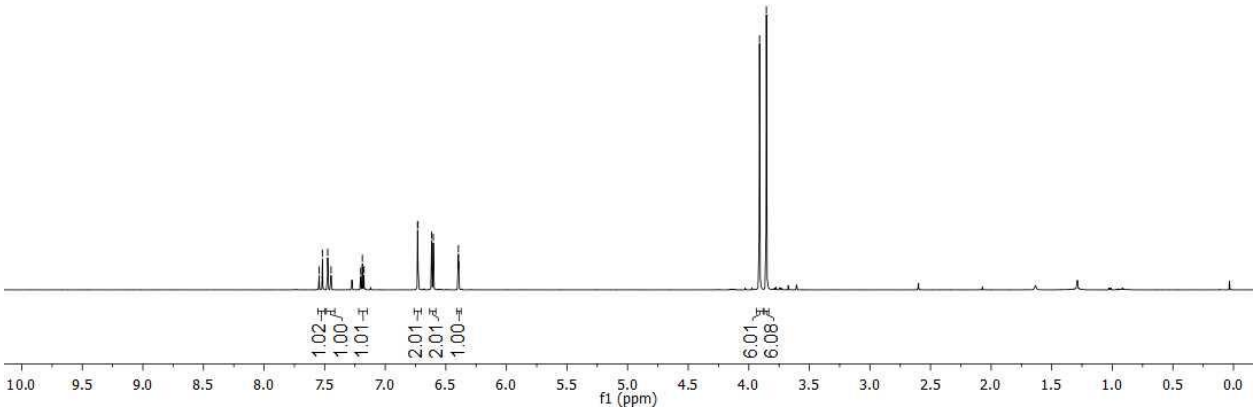

OMe
NO2
OMe
14h, Scheme 8
f1 (ppm)

FINAL NMR DATA FOR HECK/AH-463
AH-463 1H-NMR in CDCl3

7.546, 7.518, 7.475, 7.447, 7.203, 7.189, 7.175, 6.733, 6.730, 6.617, 6.603, 6.400, 6.396, 6.393, 3.911, 3.855

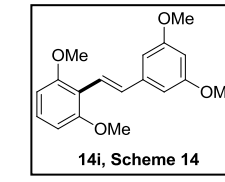



**14i, Scheme 14**

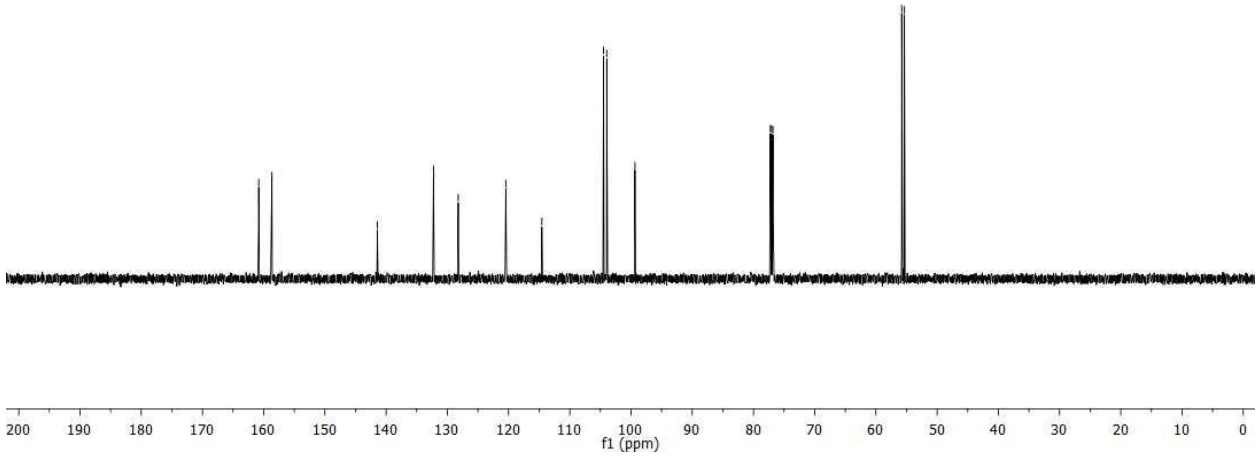



FINAL NMR DATA FOR HECK/AH-463
AH-463 13C-NMR in CDCl3

160.86, 158.65, 141.43, 132.26, 128.22, 120.45, 114.56, 104.48, 103.96, 99.35, 77.24, 77.03, 76.82, 55.79, 55.34

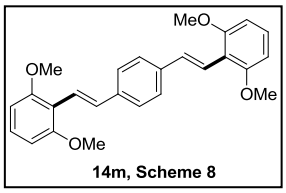



**14i, Scheme 14**

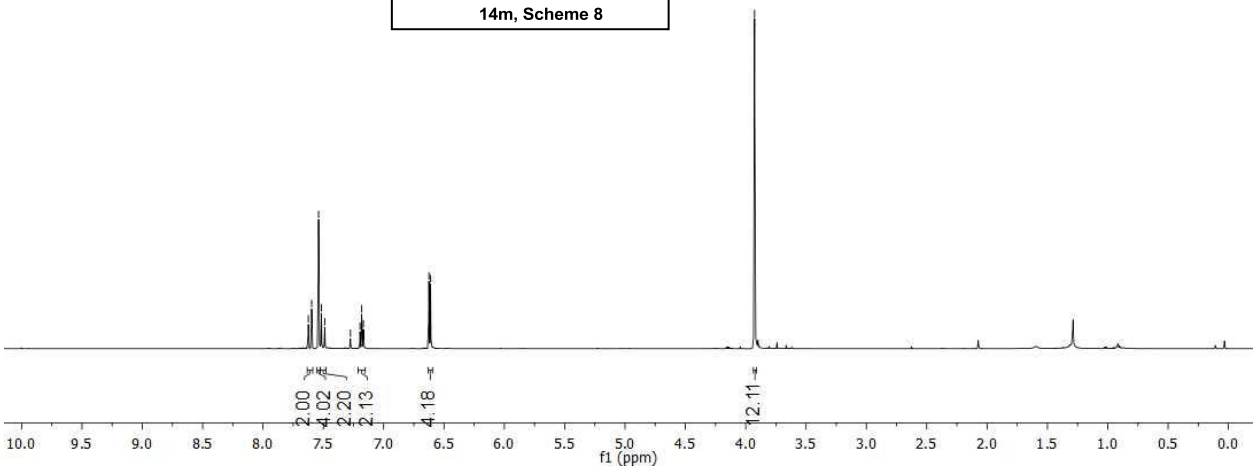


FINAL NMR DATA FOR HECK/AH-469H
AH-469 1H-NMR in CDCl3

7.629
7.597
7.540
7.516
7.488
7.275
7.196
7.182
7.168
6.625
6.611
3.927

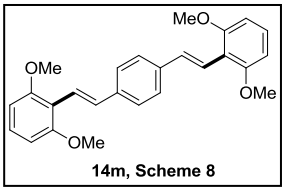



**14m, Scheme 8**

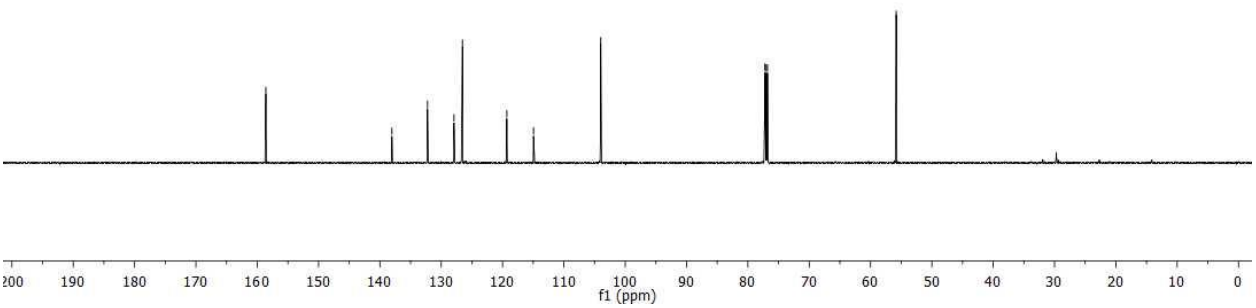



FINAL NMR DATA FOR HECK/AH-469 C
AH-469 13C-NMR in CDCl3

158.60
138.04
132.24
127.92
126.54
119.30
114.95
103.99
77.23
77.02
76.80
55.81

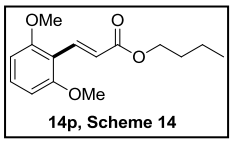



**14m, Scheme 8**

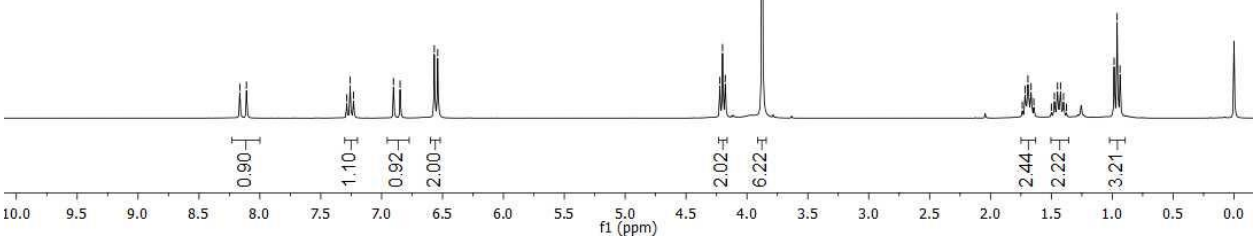


AH-449-1H/1

8.164 8.110 7.286 7.258 7.230 6.903 6.848 6.567 6.539 4.223 4.200 4.178 3.877 1.739 1.716 1.693 1.667 1.644 1.500 1.475 1.449 1.424 1.400 1.376 0.985 0.960 0.936

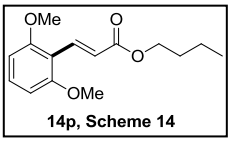



**14p, Scheme 14**

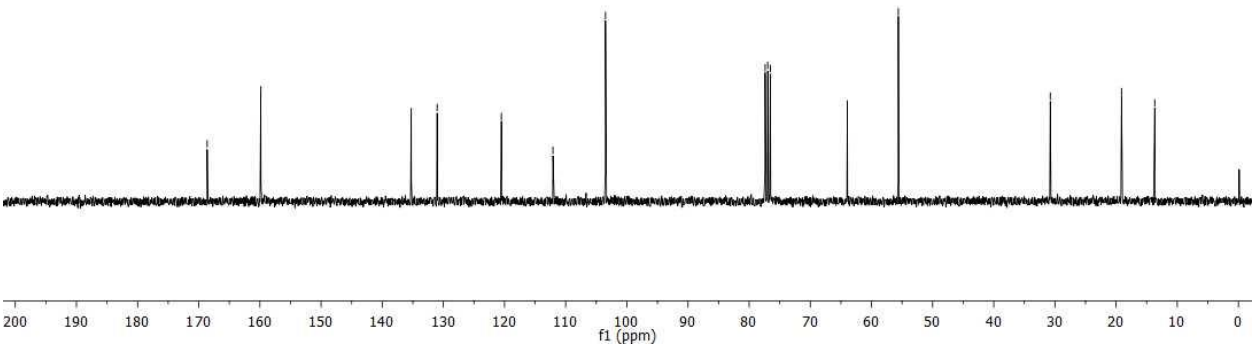


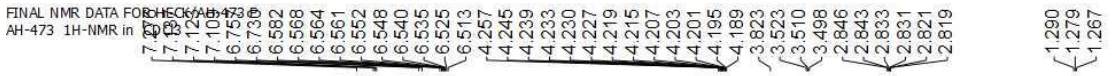

AH-449-C/1

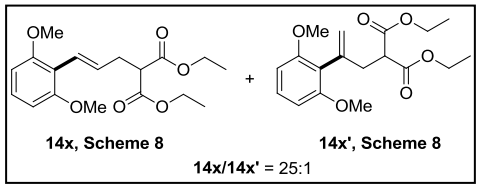
168.62 159.85 135.25 131.02 120.52 112.09 103.49 77.38 76.96 76.54 63.94 55.61 30.76 19.11 13.68




**14p, Scheme 14**





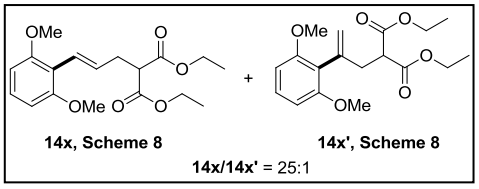




**14x, Scheme 8** **14x', Scheme 8**

**14x/14x'** = 25:1

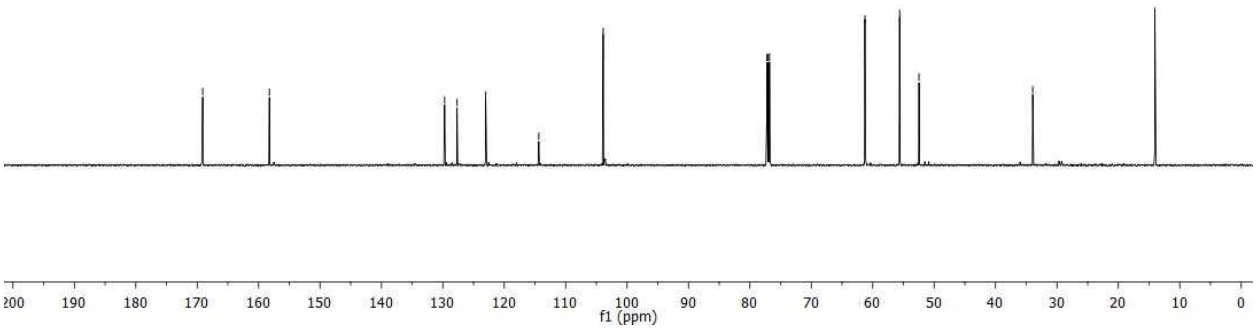






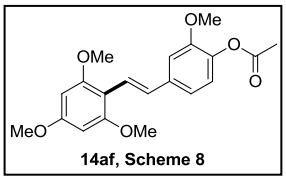

**14x, Scheme 8** **14x', Scheme 8**

**14x/14x'** = 25:1

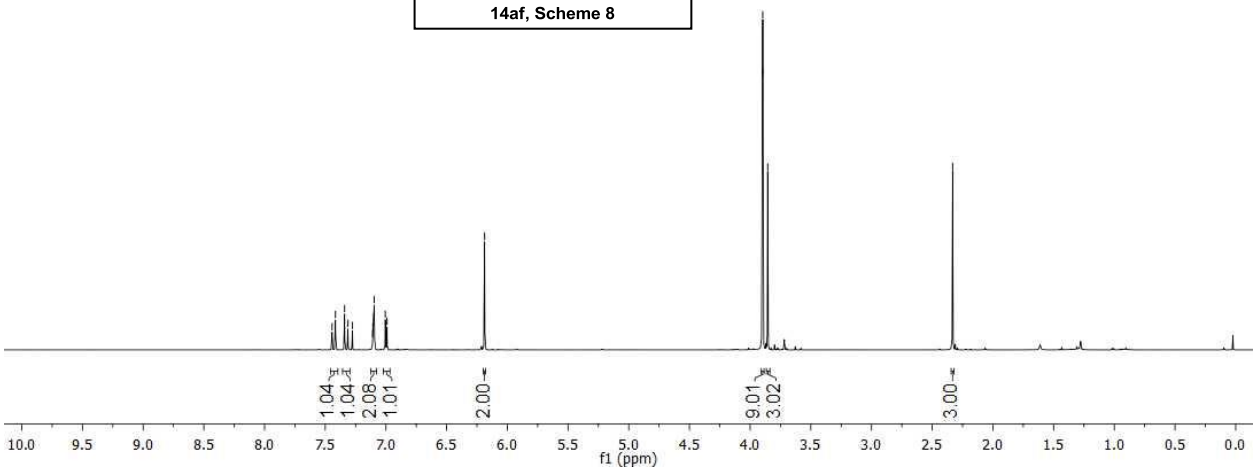


NEW NMR DATA/17
AH-511 1H-NMR in CDCl3

7.444
7.416
7.340
7.313
7.276
7.110
7.107
7.100
7.097
7.005
6.991
6.187
3.898
3.896
3.855
2.332

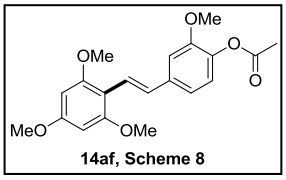



**14af, Scheme 8**

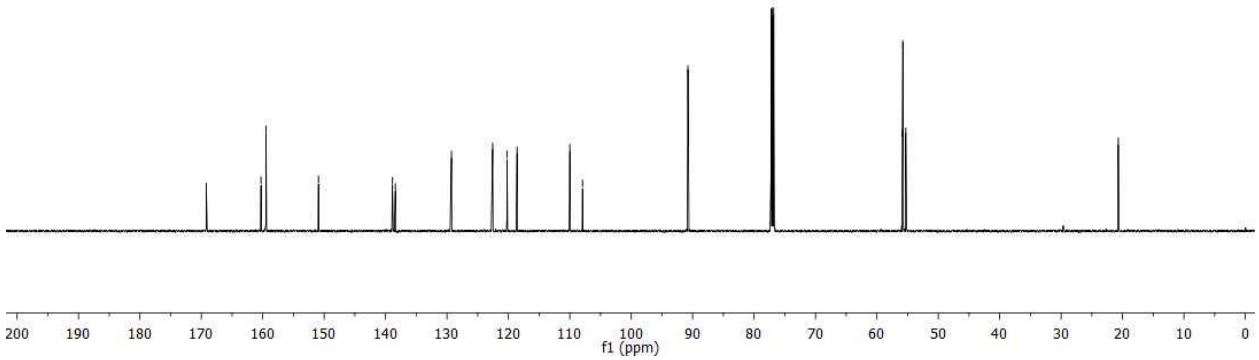



NEW NMR DATA/18
AH-511 13C-NMR in CDCl3

169.18
160.28
159.47
150.92
138.88
138.41
129.27
122.56
120.22
118.59
110.00
107.92
90.77
77.23
77.01
76.80
55.87
55.77
55.29
20.69

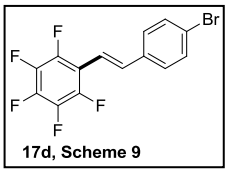



**14af, Scheme 8**

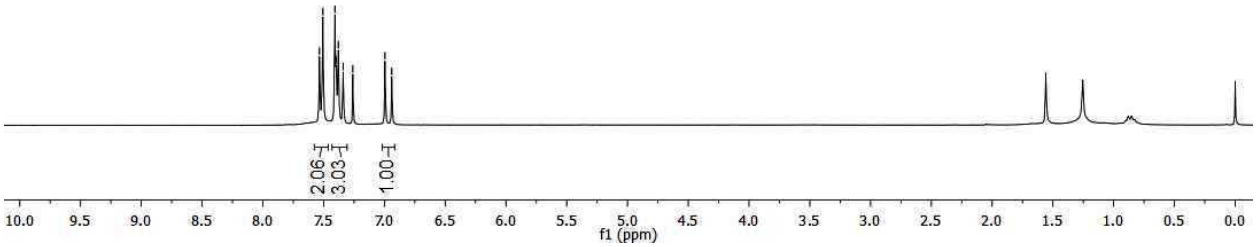


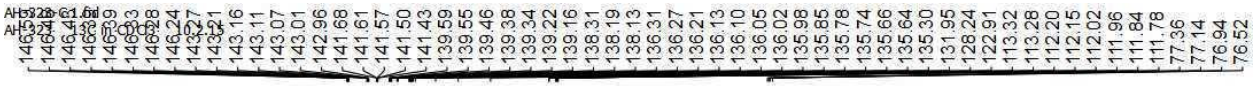
AH-323-1H.1.fid
AH-323 1H in CDCl3 29.1.15

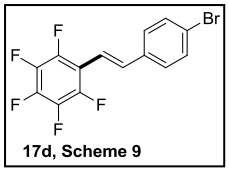
7.535
7.506
7.407
7.397
7.379
7.339
7.260
6.996
6.940



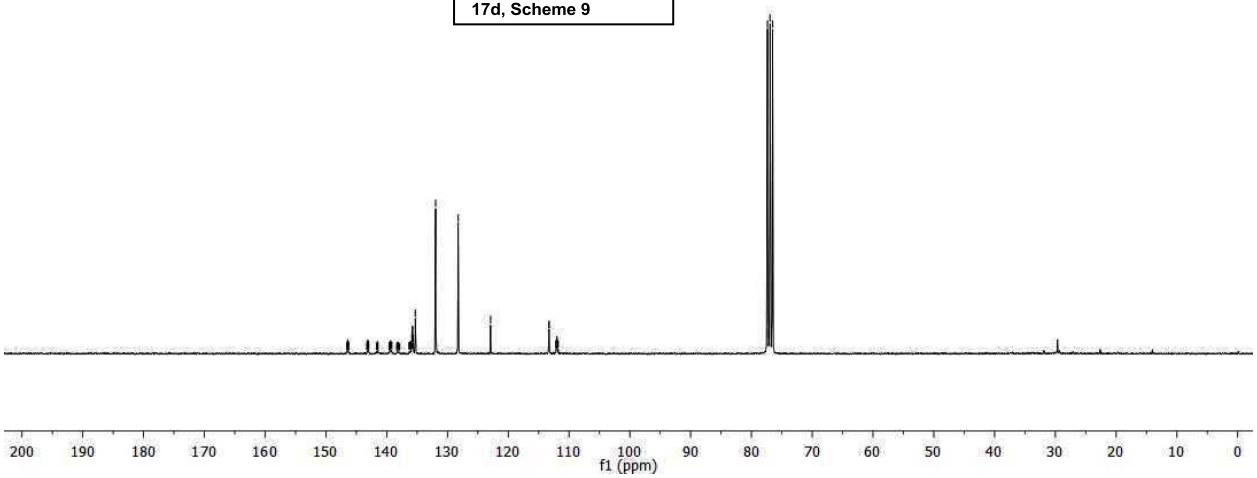

**17d, Scheme 9**




**17d, Scheme 9**



RJ-0215/1
AH-321 1H-NMR in CDCl3

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7.463
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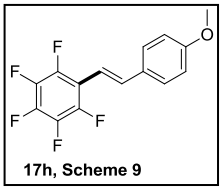
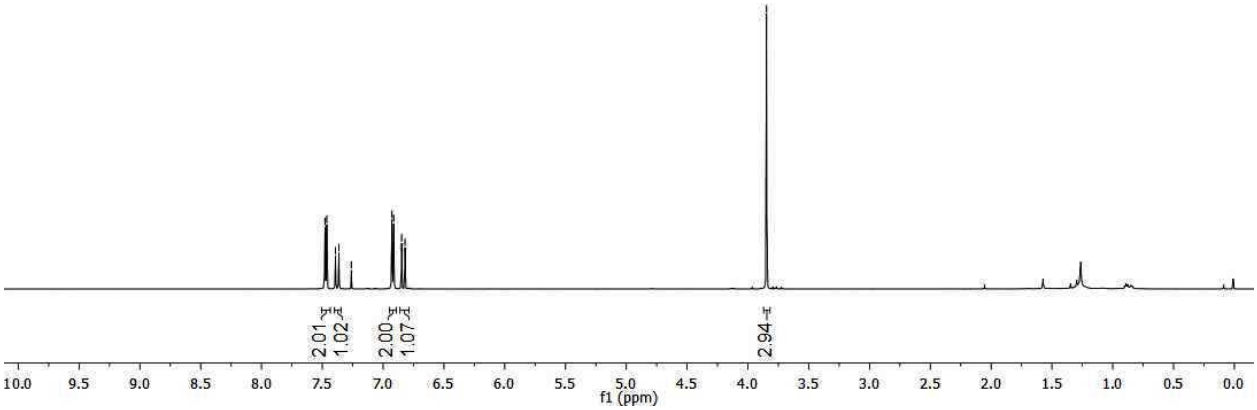
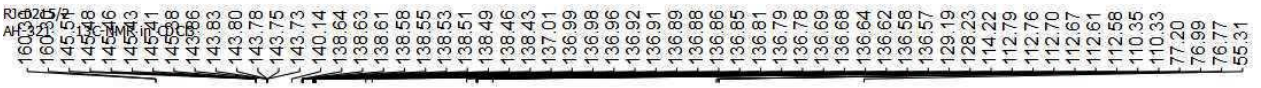
7.364
7.261
6.928
6.913
6.848
6.820

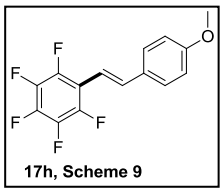
3.847



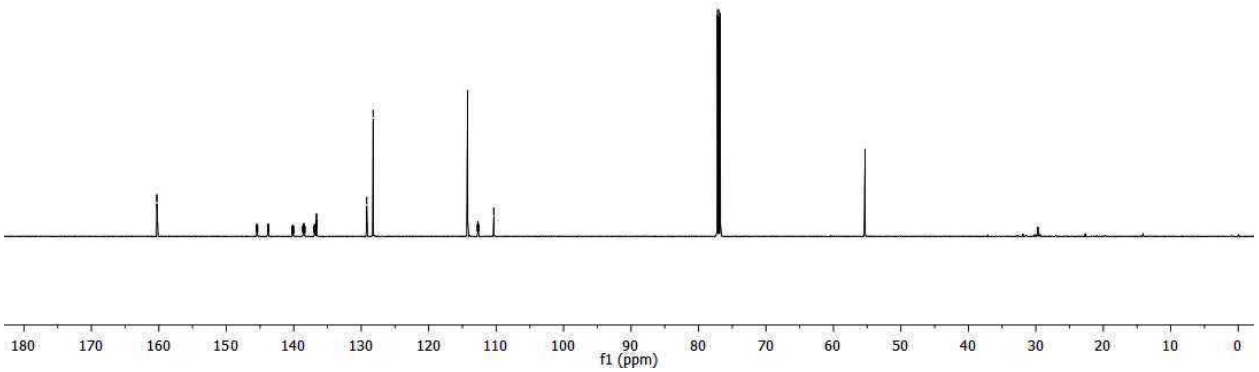

17h, Scheme 9






17h, Scheme 9



RJ-0215/15
AH-330 1H-NMR in CDCl3

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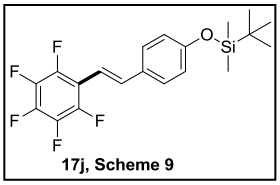
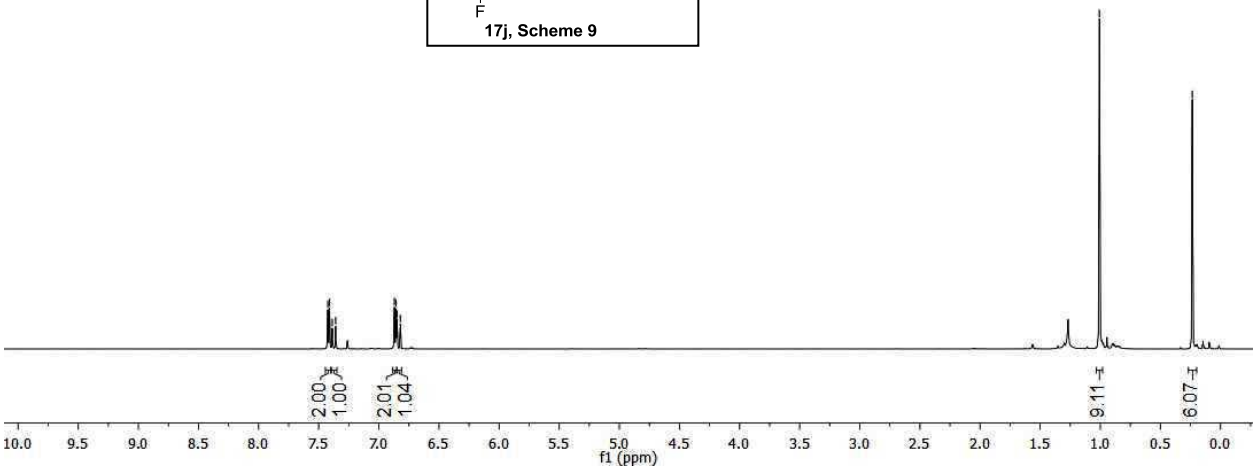
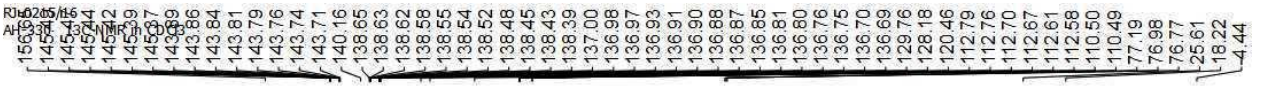
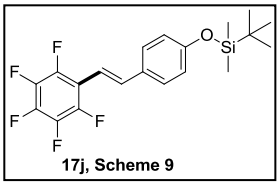
7.359
6.871
6.856
6.849
6.821
1.007
0.235




**17j, Scheme 9**



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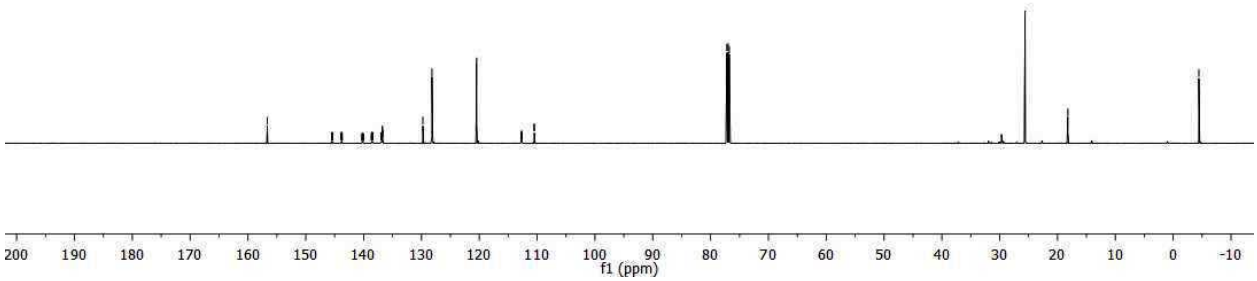

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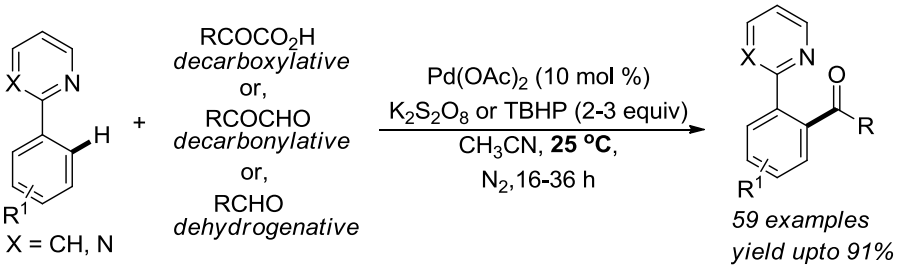
# CHAPTER IV

## Palladium-Catalyzed Decarboxylative, Decarbonylative and Dehydrogenative C($sp^2$)-H Acylation at *Room Temperature*




***Abstract:*** Over the past decades, an impressive array of C-H activation methodology has been developed for organic synthesis. However, due to the inherent inertness of the C-H bonds (e. g. ~ 110 kcal/mol for the cleavage of C(aryl)-H bonds) harsh reaction conditions have been realized to overcome high energetic transition states resulting in limited substrate scope and functional group tolerance. Therefore, development of mild C-H functionalization protocols is in high demand to exploit the full potential of C-H activation strategy in the synthesis of complex molecular framework. Although, electron-rich substrates undergo electrophilic metalation under relatively mild conditions, electron-deficient substrates proceed through a rate-limiting C-H insertion under forcing conditions at high temperature. In addition, stoichiometric amount of toxic silver salt is

frequently used in palladium catalysis to facilitate the C-H activation process which is not acceptable from environmental and industrial standpoint. We report herein, a Pd(II)-catalyzed decarboxylative C-H acylation of 2-arylpyridines with $\alpha$-ketocarboxylic acids under mild conditions. The present protocol does not require stoichiometric silver(I) salts as additives and proceeds smoothly at ambient temperature. A novel decarbonylative C-H acylation reaction has also been accomplished using aryl glyoxals as acyl surrogate. Finally, a practical C-H acylation via dehydrogenative pathway has been demonstrated using commercially available benzaldehydes and aqueous hydroperoxide. We also disclose that acetonitrile solvent is optimal for the acylation reaction at room temperature and has a prominent role on the reaction outcome. Control experiments suggest that the acylation reaction via decarboxylative, decarbonylative and dehydrogenative proceeds through radical pathway. Thus we disclose a practical protocol for the $sp^2$ C-H acylation reaction.

1. Hossian, A.; Manna, M. K.; Manna, K.; Jana, R. *Org. Biomol. Chem*. **2017**, *15*, 6592-6603.

# Palladium-Catalyzed Decarboxylative, Decarbonylative and Dehydrogenative C($sp^2$)-H Acylation at Room Temperature

## IV. 1. Introduction

Owing to the prevalence of benzophenones in natural products, pharmaceuticals and functionalized materials, the synthesis of functionalized carbonyl compounds is a sustained exertion in organic synthesis (Figure 1).[1] Typically, Lewis-acid promoted Friedel-Crafts acylation via electrophilic aromatic substitution generates isomeric mixtures and requires stoichiometric metal salts.[2] The reaction of Weinreb amides with Grignard reagents yields the carbonyl compounds with limited functional group tolerance.[3] Whereas, transition metal catalyzed cross-couplings are reported with relatively less nucleophilic organometallic reagents such as organozinc reagents and boronic acids.[4] As an alternative to air and moisture sensitive acyl chlorides which generate stoichiometric metal halide waste, thioesters is used in palladium-catalyzed Liebeskind-Srogl cross-coupling.[5] However, the reaction requires stoichiometric amount of copper complex as additive. Carbonylation of aryl halides with hazardous carbon monoxide requires special handling skills and laboratory set up.[6] Therefore, considering the stringent environmental factors (E factors) in chemical processes there is an urgent need for the development of practical and environmentally benign acylation reactions.

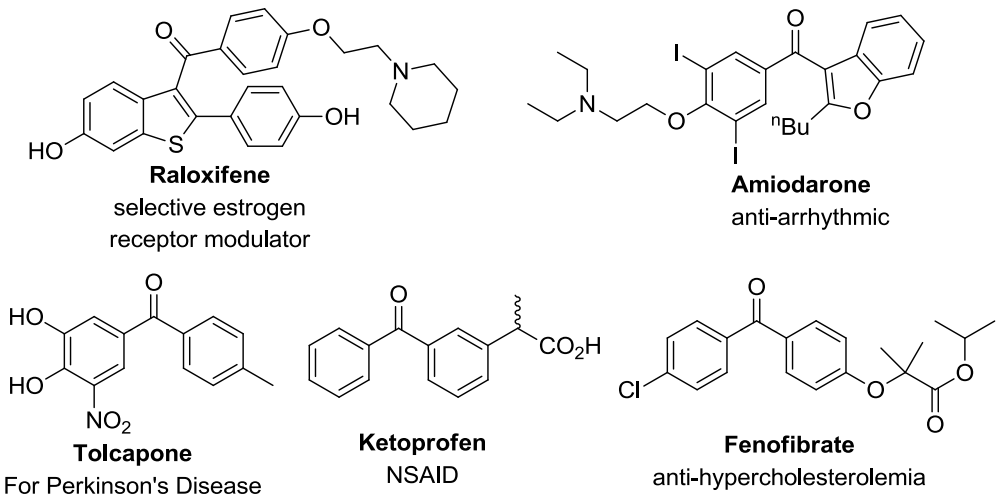
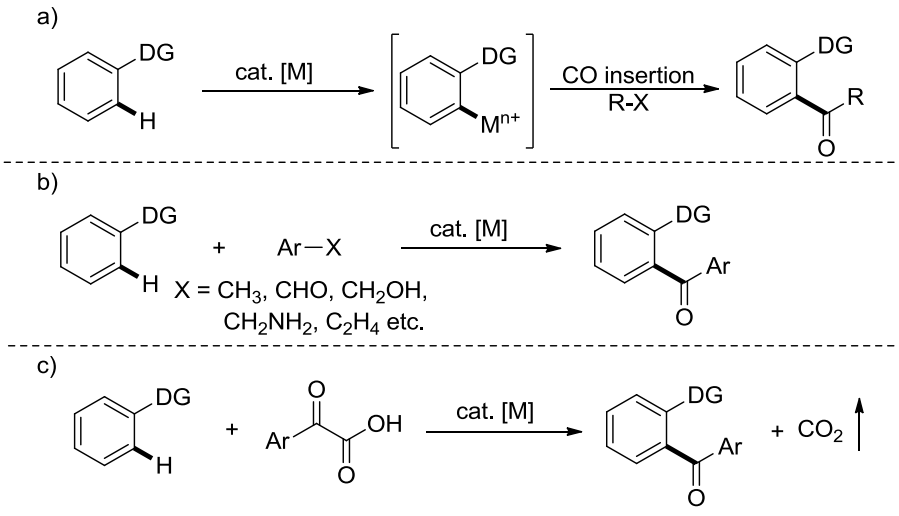



**Figure 1.** Some benzophenone containing drugs

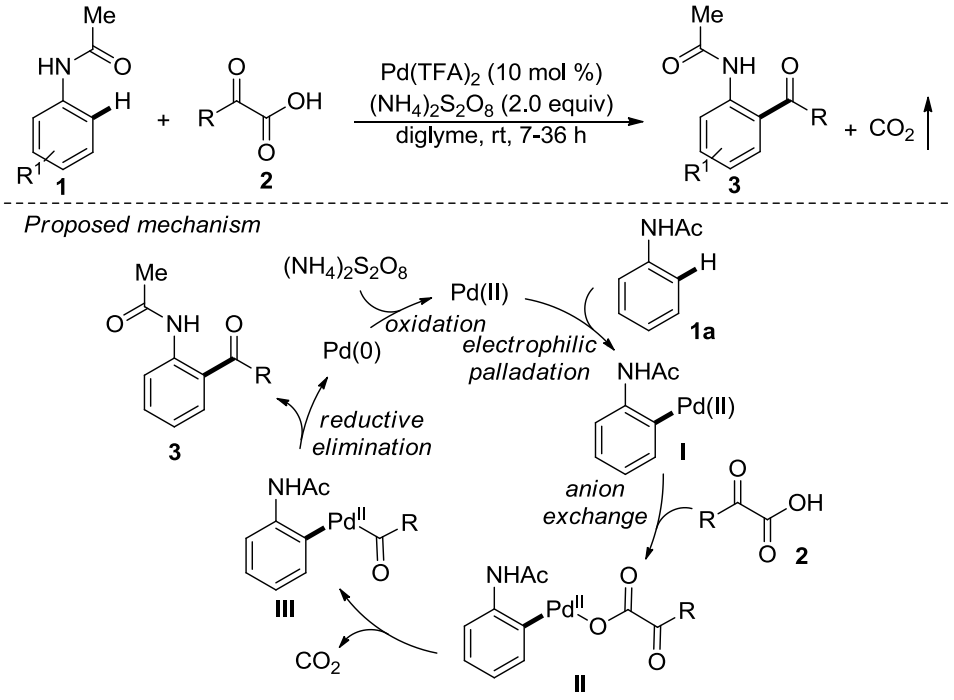
Beyond typical cross-coupling approaches, the C-H activation strategy offers a unique opportunity to access carbonyl compounds without prefunctionalization steps (Scheme 1).[7] Although an enormous effort has been dedicated to the development of C-H activation processes, significant challenges still remain unsolved. The harsh reaction conditions, use of stoichiometric toxic silver(I) salts, high reaction temperature etc. limits their application in the synthesis of complex molecular architecture and industrial processes. Thus, developments of mild acylation reaction via C-H activation processes is in high demand.[8] In recent years, decarboxylative cross-coupling has been established as a modern strategy for C-C and C-heteroatom bond formation.[9] Inexpensive and readily available carboxylic acids are used as an alternative to expensive organometallic reagents and halides. Combining the decarboxylative cross-coupling process and the C-H activation method, decarboxylative C-H functionalization has emerged as a fascinating field of research.[10] However, like C-H insertion, decarboxylative metalation is also a high energetic process and proceeds at elevated temperatures.[11] In this vein, $\alpha$-oxocarboxylic acids undergo transition metal-catalyzed decarboxylation to provide acyl anion equivalent which been utilized in cross-coupling[12] and C-H acylation reaction to provide diaryl ketones (Scheme 1).[13]




**Scheme 1.** Synthesis of carbonyl compounds via C-H bond activation methods.

## IV. 2. Review

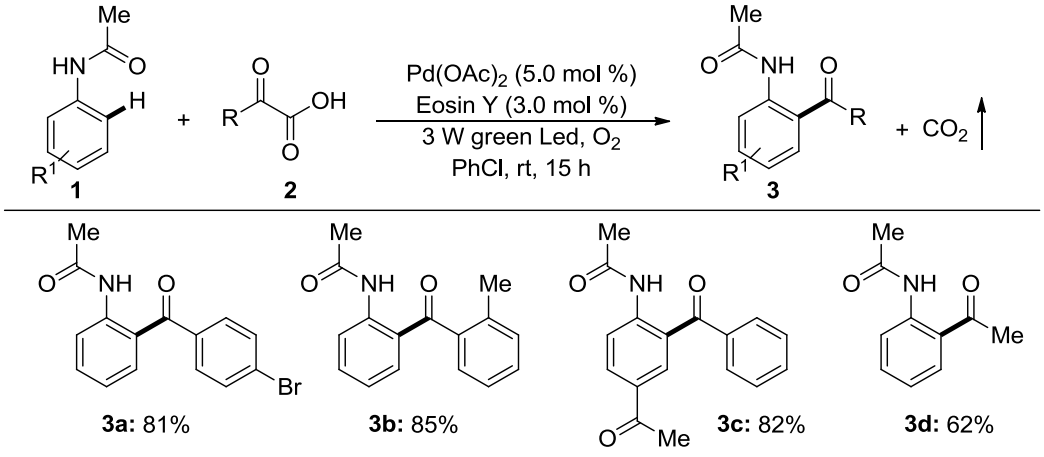
In their seminal work in 2010, the Ge group have developed a palladium catalyzed decarboxylative *ortho* C($sp^2$)-H acylation of acetanilides with $\alpha$-ketocarboxylic acids at room temperature (Scheme 2).[14] This reaction provides variety of aryl ketones with excellent yield and regioselectivity under mild conditions. Mechanistically, first *ortho*-palladation of the acetanilides occurred through a facile electrophilic *ortho* metalation pathway and subsequent anion exchange with $\alpha$-ketocarboxylates provided the intermediate **II**. Then palladium mediated decarboxylation followed by reductive elimination afforded the desired acylated product and palladium(II) catalyst is regenerated in the catalytic cycle via oxidation by oxidant $(NH_4)_2S_2O_8$.




**Scheme 2.** Palladium-catalyzed decarboxylative *ortho* acylation of acetanilides

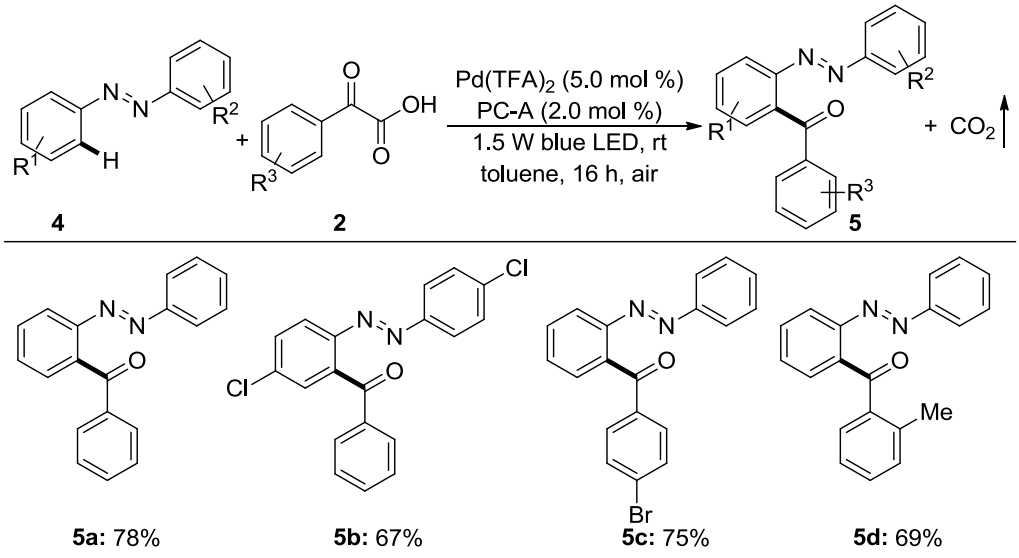
Very recently, a dual catalysis approach has been developed for the novel organic transformations via single electron transfer pathway under very mild reaction conditions.[15] The dual catalysis strategy comprising the merging of visible light induced photoredox catalysis and transition metal catalysis system has also been successfully applied to the decarboxylative acylation reactions. In this vein, the Wang group have developed a dual catalyst system merging palladium catalysis and photoredox catalysis for the decarboxylative C($sp^2$)-H acylation of acetanilides (Scheme 3).[16b] Interestingly, no

external stoichiometric oxidant is required for the catalytic turnover and molecular oxygen acts as an oxidant via superoxide radical anion formation in the reaction.




**Scheme 3.** Decarboxylative *ortho* C($sp^2$)-H acylation of acetanilides using dual catalysis

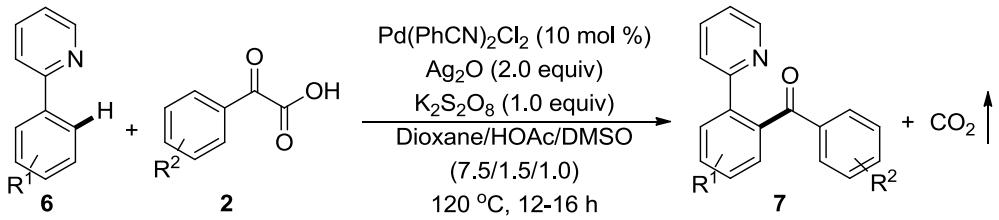
In 2016, the same group reported the decarboxylative C($sp^2$)-H acylation of azo- and azoxybenzenes with *α*-oxocarboxylic acids utilizing the dual catalysis approach through an acyl-radical intermediate (Scheme 4).[16a]



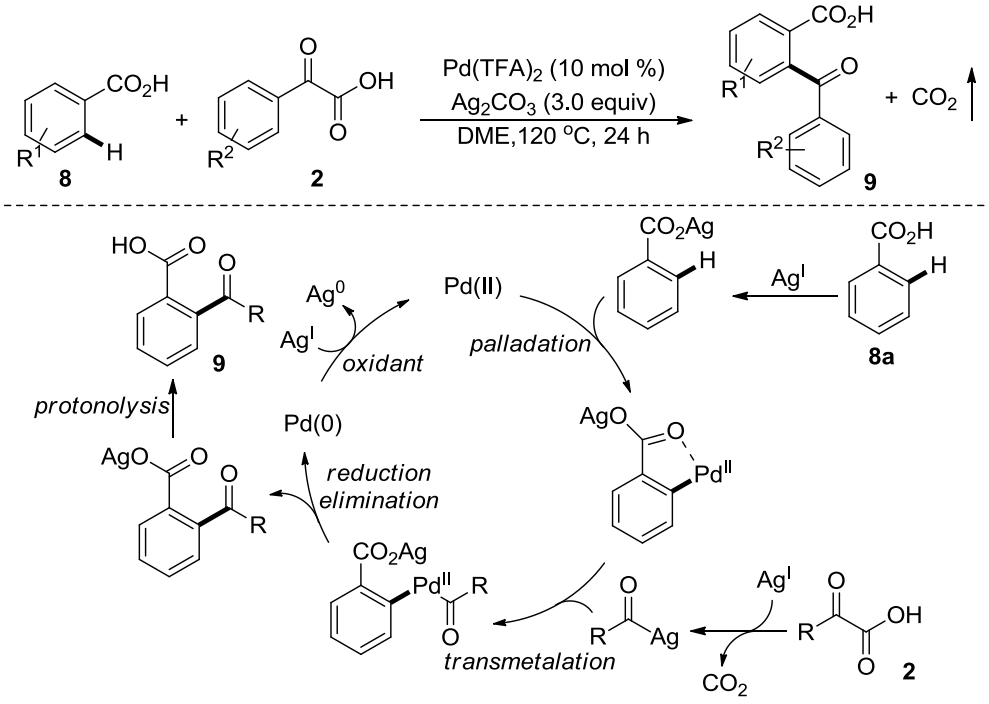

**Scheme 4.** Decarboxylative *ortho* C($sp^2$)-H acylation of azobenzene using dual catalysis

For the C($sp^2$)-H acylation reactions of electron deficient substrates, the Ge group have reported palladium-catalyzed decarboxylative C($sp^2$)-H acylation of 2-

phenylpyridines[17] (Scheme 5) and benzoic acids[18] (Scheme 6) with $\alpha$-oxocarboxylic acids. They adopted palladium/silver bimetallic catalytic system for this transformation where stoichiometric amount of silver salt was used as an oxidant as well as decarboxylation agent. These methods provided variety of aromatic ketones with excellent yields and regioselectivities.



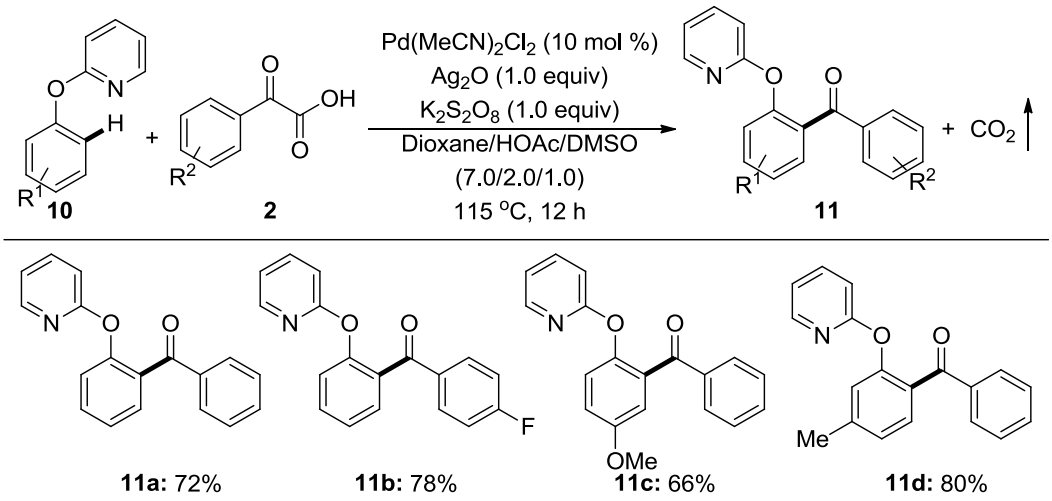

**Scheme 5.** Palladium-catalyzed decarboxylative *ortho* C($sp^2$)-H acylation of 2-phenylpyridines




**Scheme 6.** Palladium-catalyzed decarboxylative C($sp^2$)-H acylation of benzoic acids

Recently, Zhang and coworkers reported a palladium-catalyzed decarboxylative *ortho* C-H acylation of 2-aryloxypyridines with $\alpha$-oxocarboxylic acids (Scheme 7).[19] In the reaction, they have also used stoichiometric amount of silver salt as an oxidant on

palladium for catalytic turnover. The advantage of the reaction is the easy removal of the pyridine moiety from the products to give the corresponding 2-hydroxy aryl ketones which are useful precursors for the preparation of oxygen containing heterocycles.[20]

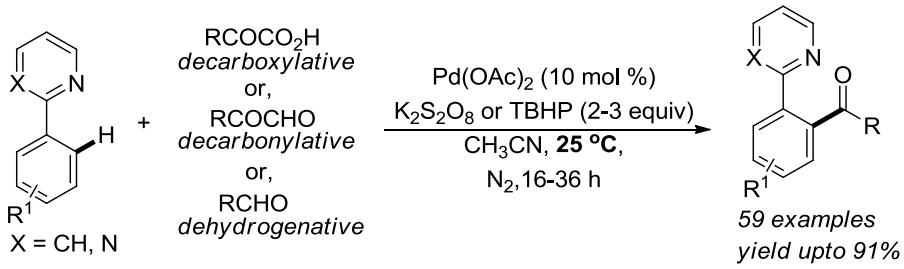



**Scheme 7.** Decarboxylative *ortho* C($sp^2$)-H acylation of 2-aryloxypyridines

## IV. 3. Present work

The decarboxylative C-H acylation of electron rich aniline derivatives or oximes proceed at ambient temperature through a facile electrophilic *ortho* metalation,[21] but electron-deficient substrates require high temperature (110-140 $^{o}$C) and stoichiometric silver(I) salt which is not acceptable from environmental and industrial viewpoint.[17,18] To the best of our knowledge, silver free decarboxylative acylation of electron-deficient 2-arylpyridine at room temperature has not been reported so far. As a part of our continuing research program for the development of cross-coupling reactions at mild conditions, we have reported decarboxylative Heck coupling at room temperature[22] and divergent synthesis of 2-arylindol and indolines via C-H activation.[23] Herein for the first time, we report a palladium-catalyzed decarboxylative C-H acylation of electron-deficient 2-arylpyridines system at room temperature. The present protocol does not require stoichiometric silver(I) salt and a dramatic influence of solvent was observed where acetonitrile was found to be optimal for this acylation reaction at ambient condition.[24] This room temperature acylation reaction was also demonstrated using phenylglyoxals

and aldehydes as acylating agent via decarbonylative and dehydrogenative manifolds respectively.



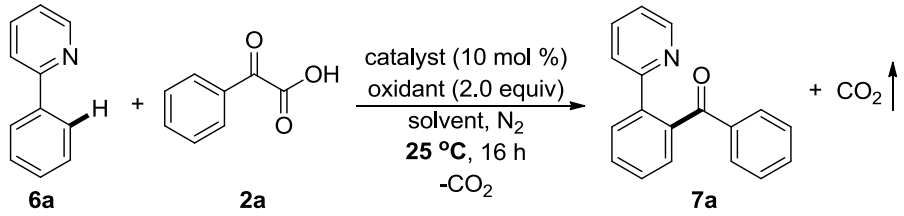

**Scheme 8.** C($sp^2$)-H acylation reaction

## IV. 4. Results and discussion

Initially, we started optimization for the decarboxylative acylation reaction at room temperature. A mixture of 2-phenylpyridine (**6a**) and phenylglyoxylic acid (**2a**) was stirred in the presence of 10 mol % palladium(II)acetate and 2.0 equiv of potassium persulfate ($K_2S_2O_8$) in diglyme solvent.[10k] The expected monoacylated product (**7a**) was obtained in 20% yield without any silver(I) salt added (entry 1, Table 1). Further screening of solvents showed that acetonitrile is superior to other solvents such as DMF, DMSO, toluene, acetic acid, 1,4-dioxane and DCE (entry 2-7, Table 1). Typically, silver salt is used in palladium catalysis for facile decarboxylation, carbonate or carboxylate anion source, halide scavenger and terminal oxidant for catalytic turnover.[25] However, contrary to our expectations, no desired product was isolated using silver salts such as $Ag_2CO_3$, $Ag_2O$ etc. at room temperature although it is used as additive for this transformation at high temperature[18a] (entry 9-10, Table 1). Other common oxidants such as ammonium persulfate, (diacetoxyiodo)benzene (PIDA), *tert*-butyl hydroperoxide (in decane) and also molecular oxygen etc. were found to be inferior for this coupling reaction (entry 11-14, Table 1). Owing to the facile electrophilic palladation of cationic palladium salts, several Pd-complexes, such as $Pd(TFA)_2$, $Pd(MeCN)_2Cl_2$, $Pd(MeCN)_2(OTs)_2$, and $Pd(MeCN)_4(BF_4)_2$ were examined but provided lower yield (entry 15-18, Table 1). We also observed that silver nitrate as a catalyst was inactive for this transformation (entry 19, Table 1). Finally, in combination of 10 mol % $Pd(OAc)_2$ and 2.0 equiv of $K_2S_2O_8$ as oxidant using acetonitrile as a solvent provided excellent

yield after stirring 16 h at room temperature (entry 8, Table 1). It is important to note that both $Pd(OAc)_2$ and $K_2S_2O_8$ are essential for this coupling reaction since no desired product was isolated while they were used separately (entry 20-21, Table 1). The yield of the acylation product was decreased to some extent under air (entry 22, Table 1) and no product was formed with oxygen purging (entry 23, Table 1). During optimization, it was found that moisture has negative impact on the reaction outcome presumably due to the formation of decarboxylative protonation product from phenylglyoxylic acid.

**Table 1.** Optimization of the reaction conditions[a,b]

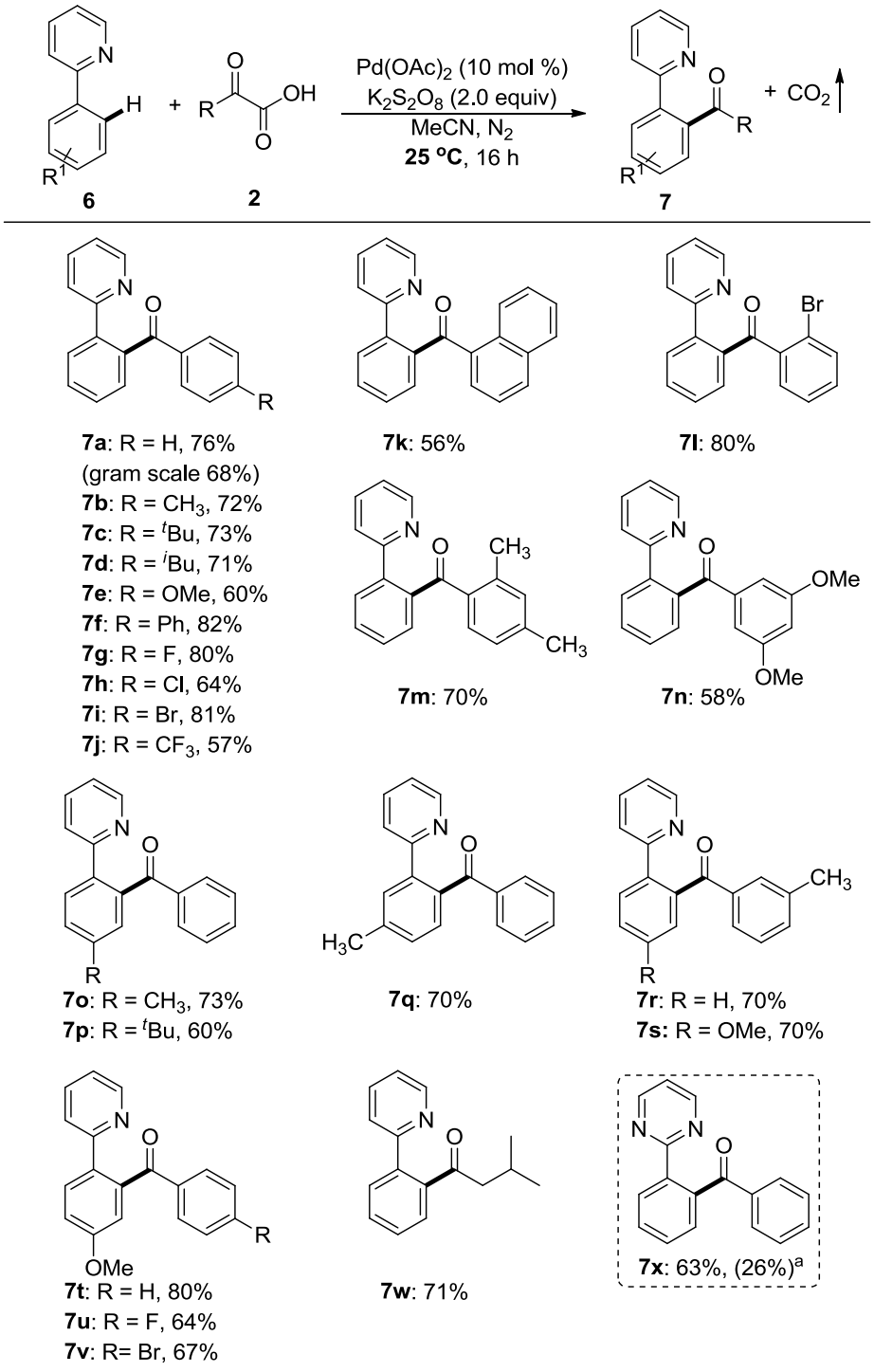



| entry | catalyst (10 mol %) | oxidant (2.0 equiv) | solvent | yield (%)[b] |
|---|---|---|---|---|
| 1 | $Pd(OAc)_2$ | $K_2S_2O_8$ | diglyme | 20 |
| 2 | $Pd(OAc)_2$ | $K_2S_2O_8$ | DMF | 50 |
| 3 | $Pd(OAc)_2$ | $K_2S_2O_8$ | DMSO | 52 |
| 4 | $Pd(OAc)_2$ | $K_2S_2O_8$ | Toluene | trace |
| 5 | $Pd(OAc)_2$ | $K_2S_2O_8$ | AcOH | 25 |
| 6 | $Pd(OAc)_2$ | $K_2S_2O_8$ | 1,4-dioxane | 14 |
| 7 | $Pd(OAc)_2$ | $K_2S_2O_8$ | DCE | 40 |
| **8** | **$Pd(OAc)_2$** | **$K_2S_2O_8$** | **MeCN** | **76** |
| 9 | $Pd(OAc)_2$ | $Ag_2CO_3$ | MeCN | 0 |
| 10 | $Pd(OAc)_2$ | $Ag_2O$ | MeCN | 0 |

| | | | | |
|---|---|---|---|---|
| 11 | $Pd(OAc)_2$ | $(NH_4)_2S_2O_8$ | MeCN | 50 |
| 12 | $Pd(OAc)_2$ | PIDA | MeCN | 26 |
| 13 | $Pd(OAc)_2$ | TBHP (in decane) | MeCN | 0 |
| 14 | $Pd(OAc)_2$ | $O_2$ | MeCN | 0 |
| 15 | $Pd(TFA)_2$ | $K_2S_2O_8$ | MeCN | 70 |
| 16 | $Pd(MeCN)_2Cl_2$ | $K_2S_2O_8$ | MeCN | 8 |
| 17 | $Pd(MeCN)_2(OTs)_2$ | $K_2S_2O_8$ | MeCN | 65 |
| 18 | $Pd(MeCN)_4(BF4)_2$ | $K_2S_2O_8$ | MeCN | 57 |
| 19 | $AgNO_3$ | $K_2S_2O_8$ | MeCN | 0 |
| 20 | $Pd(OAc)_2$ | - | MeCN | 0 |
| 21 | - | $K_2S_2O_8$ | MeCN | 0 |
| 22[c] | $Pd(OAc)_2$ | $K_2S_2O_8$ | MeCN | 67 |
| 23[d] | $Pd(OAc)_2$ | $K_2S_2O_8$ | MeCN | 0 |

[a]All reactions were carried out in 0.1 mmol scale**,** **6a** (1.0 equiv) and **2a** (1.5 equiv). [b]Yields refer to here are overall isolated yields. [c]The reaction vessel was purged with air. [d]The reaction vessel was purged with $O_2$.

Next we explored the substrate scope under the optimized reaction conditions. A wide variety of phenylglyoxylic acids having electron-withdrawing and electron-donating substituents underwent decarboxylative coupling providing high to excellent yield (Scheme 9). Besides methoxy, alkyl, and aryl groups, halogens such as bromo (**7i, 7l, 7v,** Scheme 9), chloro (**7h**, Scheme 9), and fluoro (**7g**, Scheme 9) were also well tolerated in the reaction condition which are useful for further cross-coupling reactions. A strong electron-withdrawing group on *α*-keto acid afforded the acylated product in good yield (**7j**, Scheme 9). Interestingly, the *α*-keto acid with a naphthyl moiety furnished the



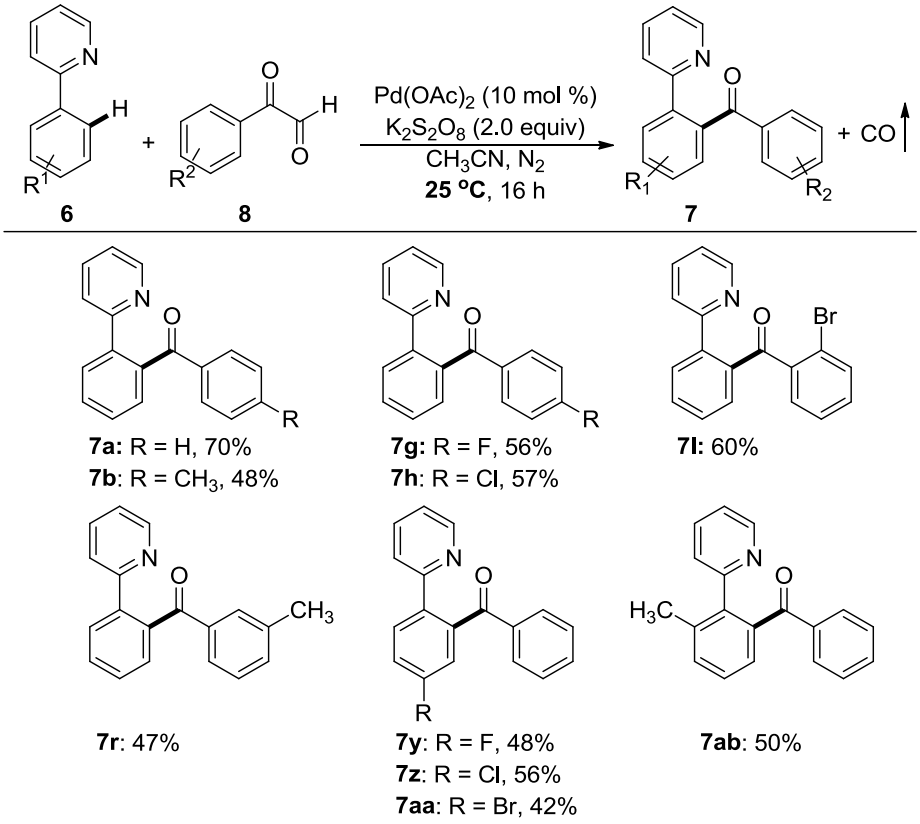

**Scheme 9.** Substrate scope of 2-phenylpyridines and *α*-ketocarboxylic acids

*Note*: The reaction was carried out in 0.2 mmol scale, **6** (1.0 equiv) and **2** (1.5-2.0 equiv). The yield referred to here is the average isolated yield of at least two experiments. [a]Diacylation occurred.

desired product in good yield (**7k**, Scheme 9). The *ortho* substituted $\alpha$-keto acid participated in the reaction with excellent yield (**7l**, Scheme 9). Disubstituted $\alpha$-keto acids also participated in the reaction providing good yield (**7m**-**7n**, Scheme 9). No significant influence of the electronic nature of the substituents on $\alpha$-keto acids was observed on the reaction outcome. Similarly, substitutions on the 2-phenylpyridine moiety such as alkyl **(7o**-**7q**, Scheme 9), methoxy (**7s**-**7v**, Scheme 9) were tolerated in the reaction condition. In addition, aliphatic $\alpha$-oxocarboxylic acid also afforded the desired product in good yield (**7w**, Scheme 9). Unfortunately, electron deficient groups like acyl, trifluromethyl on 2-phenylpyridine moiety did not furnish any acylated products. Other nitrogen directing groups like 2- phenoxypyridine, 1-phenyl-1*H*-pyrazole, acetophenone *O*-methyl oxime, and also 2-phenylbenzo[*d*]thiazole did not provide desired acylation products at room temperature. However, 2-phenylpyrimidine furnished a mixture of mono and diacylation product which was separated through column chromatography (mono:di = 2.5:1). To demonstrate the practical utility of this present protocol the reaction was performed in gram-scale providing the acylation product in comparable yields (**7a**, Scheme 9).

In recent years, decarbonylative cross-coupling reaction from carbonyl or carboxylic acid derivatives has emerged as a promising strategy in organic synthesis.[26] Initially, the transition metal undergoes oxidative addition to the activated carboxylic acid derivatives such as acid chlorides,[27] anhydrides,[28] esters[29] etc. to generate an acyl-metal species. Subsequently, aryl-metal species is formed through the extrusion of carbon monoxide. Unlike redox-neutral decarboxylative cross-coupling, no stoichiometric oxidant is required in the decarbonylative cross-coupling process. Although transition metal-catalyzed decarbonylative cross-coupling for arylation has been explored[30] but decarbonylative C-H acylation is not known. We hypothesized that glyoxals can be utilized in palladium-catalyzed decarbonylative C-H acylation reaction. To test, a mixture of 2-phenylpyridine, (**6a**) and phenylglyoxal (**8a**) was subjected under the optimized reaction conditions of decarboxylative acylation. Gratifyingly, the corresponding acylation product was isolated in 70% yield (**7a**, Scheme 10). However, the reaction under oxygen did not furnish any acylation product although dioxygen-mediated generation of alkyl radical from corresponding aldehydes is known at elevated temperature.[31] Other oxidants such as aq. TBHP or TBHP in decane even $(NH_4)_2S_2O_8$

were ineffective for this transformation. Surprisingly, a trace amount of acylation product was isolated in other solvents like DMSO, DMF, DCE and toluene. Therefore, we proceeded to examine the substrate scope under this condition. To our delight, a number of 2-phenylpyridine as well as phenylglyoxal with different substituents provided the corresponding acylated product with moderate to good yield (Scheme 10). It is noteworthy that halogenated and *ortho*-substituted 2-phynylpyridines also provided moderate yield of the acylation products which were ineffective under decarboxylative acylation protocol.



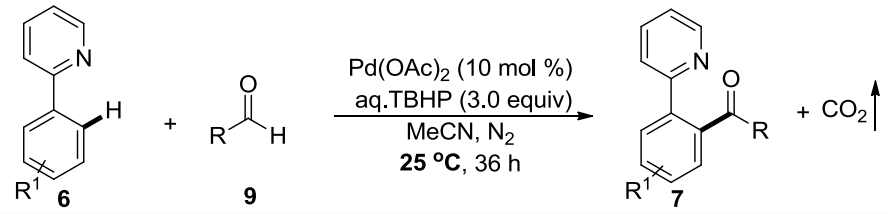

**Scheme 10.** Substrate scope of 2-phenylpyridines and 2-oxo-2-phenylacetaldehydes

*Note*: The reaction was carried out in 0.2 mmol scale, **6** (1.0 equiv) and **8** (1.5 equiv). The yield referred to here is the average isolated yield of at least two experiments.

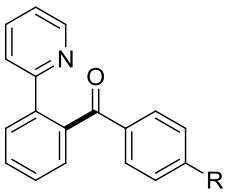
Next we turned our attention to achieve acylation reaction with commercially available and inexpensive aldehydes as acylation agent. From literature, palladium-catalyzed C-H acylation of 2-phenylpyridine with aryl and alkyl aldehydes is known at

high temperature.[32] However, aldehydes are converted to the corresponding acids by oxygen rapidly at high temperature and the yield is decreased.[32b,33] In addition, the oxidant TBHP is explosive at high temperature particularly in industrial-scale.[24] Keeping this in mind we intended to develop an acylation reaction with aldehydes at *room temperature*. Our initial trial reaction between 2-phenylpyridine (**6a**) and benzaldehyde (**9a**) under the previous optimized reaction conditions afforded acylated product in 35% yield (**7a**, Scheme 11). Considering the unique ability of *tert*-butylhydroperoxide (TBHP) to generate acyl radical from aldehydes,[35] we decided to use TBHP as oxidant in lieu of $K_2S_2O_8$. Surprisingly, the yield was improved to 55% with inexpensive aq. TBHP. Finally an excellent yield of the acylated product (**7a**) in 87% was isolated after stirring the reaction mixture for 36 h at room temperature with the combination of 10 mol % $Pd(OAc)_2$ and 3.0 equiv of aq. TBHP from 1.0 equiv of 2-phenylpyridine (**6a**) and 1.5 equiv of benzaldehyde (**9a**). However, 30% aq. $H_2O_2$ in lieu of aq. TBHP did not furnish any acylation product. To note, the reaction under air or oxygen provided lower (37%) or no yield thus the reaction vessel was purged with nitrogen. The reaction under neat condition also furnished inferior result (38%).

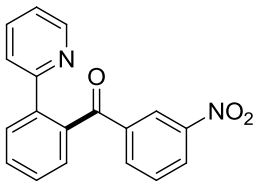
Subsequently, we explored the substrate scope under the optimized reaction conditions. A wide variety of functional groups on 2-phenylpyridine as well as on aldehyde were found to be compatible under this mild reaction protocol. Besides methoxy, alkyl, and aryl groups, halogens such as chloro (**7ah**, Scheme 11), ester (**7ad**, Scheme 11), cyano (**7ae**, Scheme 11), nitro (**7af**, Scheme 11) remain intact which are useful for further organic transformation. Interestingly, the acyl group on aldehyde (**7ac**, Scheme 11) is well-tolerated under the reaction conditions which demonstrate the mild nature of the conditions. Interestingly, the aldehyde with a naphthyl moiety furnished the desired product in good yields (**7ag**, Scheme 11). The electron deficient group like acyl on 2-phenylpyridine afforded the moderate yield (**7an**, Scheme 11) which was inferior in the decarboxylative acylation reaction. The reaction with 2-phenylquinoline afforded the acylation product in moderate yield (**7ao**, Scheme 11). Interestingly, the heterocyclic aldehydes, such as furan-2-carbaldehyde and thiophene-3-carbaldehyde provided moderate yield of the desired product (**7ap**-**7aq**, Scheme 11). In addition, aliphatic aldehydes also afforded the acylation product in moderate to excellent yield (**7w**-**7as**,



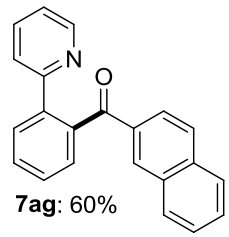

**6** **9** **7**



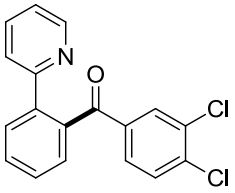
**7a**: R = H, 87%
(gram scale 72%)
**7b**: R = $CH_3$, 78%
**7e**: R = OMe, 68%
**7ac**: R = Ac, 73%
**7ad**: R = COOMe, 72%
**7ae**: R = CN, 47%



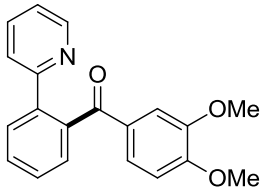
**7af**: 56%



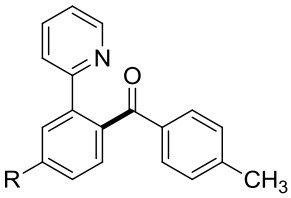
**7ag**: 60%



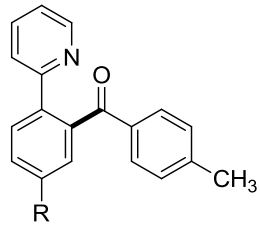
**7ah**: 48%



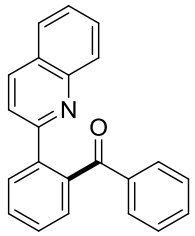
**7ai**: 75%



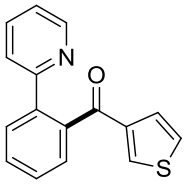
**7aj**: R = $CH_3$, 80%
**7ak**: R = OMe, 60%



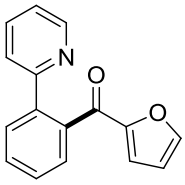
**7al**: R = $CH_3$, 70%
**7am**: R = Ph, 55%
**7an**: R = Ac, 45%



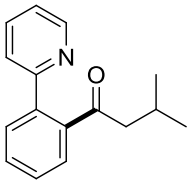
**7ao**: 46%



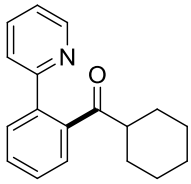
**7ap**: 56%



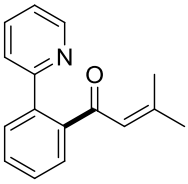
**7aq**: 42%



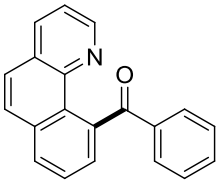
**7w**: 65%



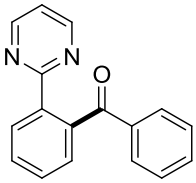
**7ar**: 88%



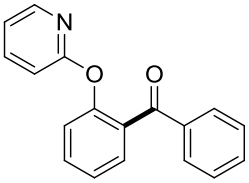
**7as**: 32%



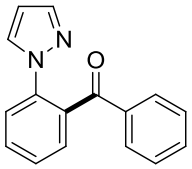
**7at**: 91%



**7x**: 65%



**7au**: 22%[a]



**7av**: 32%

**Scheme 11.** Substrate scope of 2-phenylpyridines and aldehydes

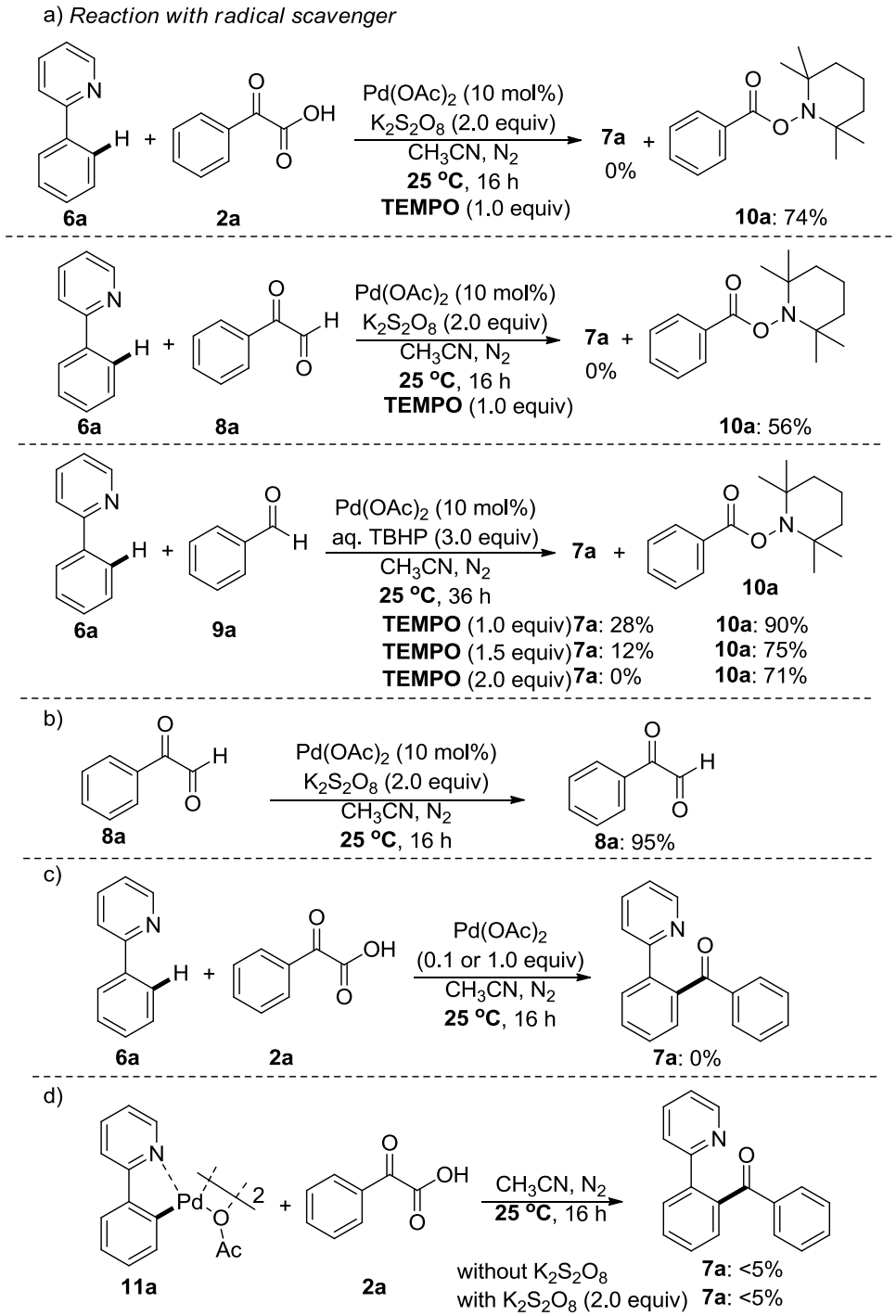
*Note*: The reaction was carried out in 0.2 mmol scale, **6** (1.0 equiv) and **9** (1.5 equiv). The yield referred to here is the average isolated yield of at least two experiments. [a]The reaction was run for 72 h.

Scheme 11). It is important to note that, benzo[*h*]quinoline worked extremely well in the reaction conditions to give the corresponding acylation product in excellent yield (**7at**, Scheme 11). Although, 2-phenoxypyridine, 1-phenyl-1*H*-pyrazole provided lower yield and unreacted starting material was recovered (**7au**-**7av**, Scheme 11) but 2-phenylpyrimidine furnished good yield (**7x**, Scheme 11) of the mono-acylation product. Finally, the reaction was reproduced in gram-scale providing comparable yield (**7a**, Scheme 11). Other *in situ* convertible acylating agents such as benzyl alcohol, benzyl amine, styrene and toluene did not furnish any acylated product with 2-phenylpyridine under the reaction conditions.

## IV. 5. Reaction mechanism

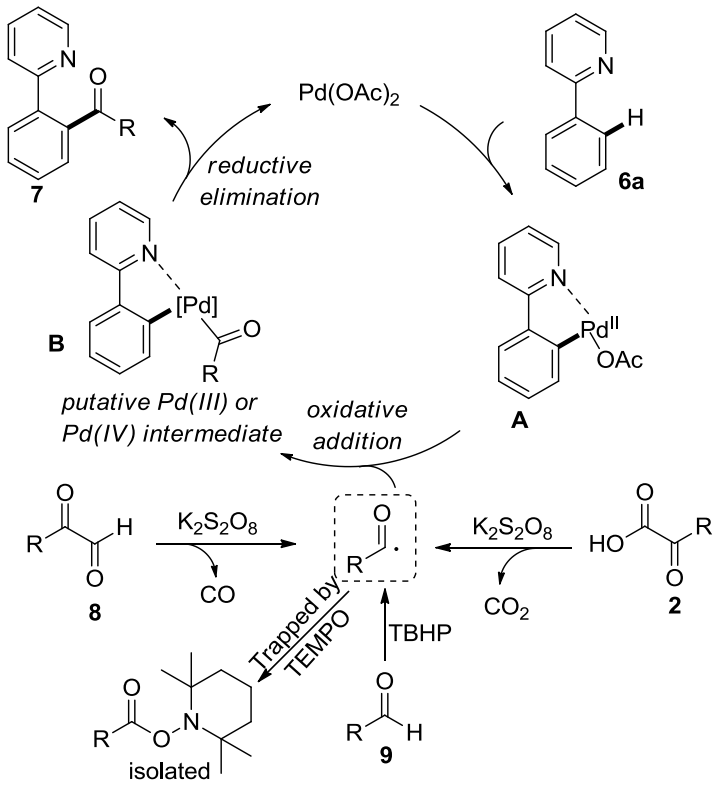
To gain insight into the reaction mechanism, we performed several control experiments. To check whether decarboxylative acylation reaction with phenylglyoxylic acid proceeds through radical or anionic pathway, radical scavenger 2,2,6,6-tetramethylpiperidinyl-1-oxy (TEMPO) experiment was performed. It was observed that the acylation reaction completely suppressed with 1.0 equiv of TEMPO. The TEMPO-acyl adduct, 2,2,6,6-tetramethylpiperidin-1-yl benzoate (**10a**) was detected in electrospray ionization (ESI) mass spectrometry of the crude reaction mixture. Further, it was isolated in 74% yield and well-characterized by NMR and HRMS spectroscopy (Scheme 12a). Thus the decarboxylative acylation reaction may proceed through radical pathway and the acyl radical may generate from the corresponding phenylglyoxylic acids with $K_2S_2O_8$ at room temperature. Similarly, acylation reaction with phenylglyoxal was also completely suppressed with 1.0 equiv of TEMPO and the TEMPO-acyl adduct (**10a**) was isolated in 56% yield (Scheme 12a). In addition, phenylglyoxal did not oxidized to the phenylglyoxylic acid under the reaction condition and remained intact (Scheme 12b). Therefore, the possibility of oxidation to the corresponding acid followed by

decarboxylative acylation was ruled out rather an acyl radical may generate in the course of the reaction through decarbonylation of the arylglyoxal. Finally, dehydrogenative




**Scheme 12.** Control experiments

acylation reaction with benzaldehyde was also supressed substantially with 1.0 and 1.5 equiv of TEMPO and completely suppressed with 2.0 equiv of TEMPO. The TEMPO-acyl adduct (**10a**) was also isolated in 71% yield for further confirmation (Scheme 12a). Thus, dehydrogenative acylation may also proceed through radical pathway and the acyl radical intermediate may form from the corresponding benzaldehyde *via* TBHP oxidation. In the absence of $K_2S_2O_8$ no decarboxylative acylation product was isolated with 10 mol % or even with 1.0 equiv of $Pd(OAc)_2$ indicating that combination of palladium and $K_2S_2O_8$ is essential for the reaction to occur (Scheme 12c). Since palladium(II) acetate is known to form a dimeric complex with 2-phenylpyridine through C-H insertion,[36] a palladium dimer complex (**11a**) was prepared separately and subjected to the reaction conditions (Scheme 12d). Only a trace amount of product was detected suggesting that dimeric palladium species with 2-phenylpyridine may not form under the present reaction conditions whereas a monomeric palladium species may be involved.




**Scheme 13.** Plausible mechanism

From the control experiments and previous reported literatures,[35,37,38] we propose the reaction mechanism which has shown in Scheme 13. The pyridine-assisted cyclopalladation with Pd(II) *via* electrophilic palladation may generates the 5-membered palladacycle intermediate **A** (Scheme 13), which undergoes oxidative addition with acyl radical to yield cyclopalladated Pd(III) intermediate **B** (Scheme 13). Under visible light photoredox and palladium dual catalysis condition this putative Pd(III) is further oxidized to Pd(IV) with photoredox catalyst and/or oxidant.[8e,21b,38c,d,39] However in these catalytic systems, the role of $K_2S_2O_8$ or TBHP in Pd(III)/Pd(IV) oxidation is not clear at this moment and warrants further investigation. The desired acylation product **3** may form through the facile reductive elimination of the intermediate **B** (Scheme 13) and the generation of Pd(II) catalyst for the subsequent runs.

## IV. 6. Conclusion

In conclusions, we have developed a mild reaction protocol for Pd(II)-catalyzed C($sp^2$)-H acylation using *α*-ketocarboxylic acids, phenylglyoxals and commercially available, inexpensive aldehydes via decarboxylative, decarbonylative and dehydrogenative manifolds respectively. The major advantages of the present protocol are- a) the reaction operates under mild conditions at *room temperature*; b) it does not require stoichiometric amount of toxic silver(I) salt for decarboxylation of the *α*-ketocarboxylic acid or as oxidant; c) acetonitrile was optimal for the acylation; d) gaseous $CO_2$, CO or water is formed as by-products avoiding rigorous separation technique; e) the present acylation reaction proceeds through radical pathway to provide mono acylation product at the *ortho* position selectively. This room temperature acylation reaction is scalable, energy efficient and avoids the accidental hazard due to explosion of peroxides at elevated temperature. Thus, we anticipate that this mild C-H acylation protocol will find its place in industrial application.

## IV. 7. Experimental section

**General experimental procedure for the preparation of 2-phenylpyridines.[40]**

To a solution of arylboronic acid (2.6 mmol, 1.3 equiv) in toluene (7.0 mL), ethanol (1.5 mL) and $H_2O$ (7.0 mL) $Na_2CO_3$ (1.6 g, 15 mmol, 7.5 equiv) was added followed by $Pd(PPh_3)_4$ (69 mg, 0.060 mmol) and 2-bromopyridine (0.2 mL, 2.0 mmol, 1.0 equiv) were added in a 50 mL round bottom flask. The reaction mixture was evacuated and refilled with nitrogen three times and stirred at 110 $^oC$ for 18 h. After the completion of the reaction as indicated by TLC, the reaction mixture was cooled to room temperature. To the reaction mixture, aqueous $NH_4CL$ (15 mL) was added, extracted with ethyl acetate for three times, dried over $Na_2SO_4$ and evaporated in vacuum to afford the crude product. The crude product was purified by column chromatography on silica gel with using hexane/EtOAc (9/1) to afford pure 2-arylpyridines.

**General experimental procedure for the preparation of arylglyoxylic acids.[41]**

A mixture of acetophenones (8.0 mmol, 1.0 equiv) and selenium dioxide (1.8 g, 16 mmol, 2.0 equiv) in dry pyridine (4.0 mL) was stirred at 120 $^oC$ under $N_2$ for 18 h. After completion of the reaction, as determined by TLC, the solution containing precipitated selenium was filtered using a Buckner funnel and the residue was washed with ethyl acetate (40 mL). The combined filtrate was treated with 1N HCl (60 mL), the organic layer was separated, and the remaining aqueous layer was extracted with ethyl acetate (2x20). The organic layers were combined and treated with 1N NaOH (2x50), and the aqueous layer was separated. Then the aqueous layer was acidified using 1N HCl to about pH 1.5. The mixture was extracted with ethyl acetate (3x40), and the combined organic layers were dried over $Na_2SO_4$ and evaporated in vacuum to afford the crude product. The crude product was purified by column chromatography on silica gel with using hexane/EtOAc (7/3) to give the pure corresponding arylglyoxylic acids.

**General experimental procedure for the preparation of phenylglyoxals.[42]**

To a 50 mL two-neck round bottom flask fitted with a condenser, was added 1,4-dioxane (13.0 mL), $SeO_2$ (2.8 g, 25.0 mmol) and water (0.5 mL). The mixture was heated at 50-55 $^oC$ and stirred under $N_2$ atmosphere until the solid was dissolved, then the corresponding acetophenone (25.0 mmol, 1.0 equiv) was added and the reaction mixture was stirred at 110 $^oC$ for 4 h. Then the reaction mixture was cooled to room temperature. The solid was

removed by filtration; the filtrate was evaporated to afford a crude product. The crude product was purified by silica gel column chromatography (hexane:ethyl acetate/8:2) to give the product as a yellow liquid. This liquid was dissolved in hot water (10 mL) and allowed to crystallize to afford the desired products, arylglyoxal monohydrate as a white solid.

**Experimental procedure for the preparation of 2-phenylpyrimidine.[43]**

To a round-bottom flask was added 2-chloropyrimidine (229.0 mg, 2.0 mmol, 1.0 equiv), phenylboronic acid (293mg, 2.4 mmol, 1.2 equiv), $Pd(PPh_3)_2Cl_2$ (28mg, 0.04 mmol, 0.02 equiv) and $Na_2CO_3$ (2.0 M, 5.0 mL) in dioxane (5.0 mL). The reaction mixture was heated to 90 $^oC$ for 16 h under $N_2$ atmosphere. After completion of the reaction (as indicated by TLC), the heterogeneous aqueous was concentrated under reduced pressure and the residue was extracted with EtOAc (30 mL), washed by $H_2O$ (30 mL) and brine (30 mL). The organic layer was dried over $Na_2SO_4$, concentrated and purified by column chromatography on silica gel using ethyl acetate/hexane as eluent to afford the desired product, 2-phenylpyrimidine as colorless oil. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 8.81 (d, $J$ = 4.8 Hz, 2H), 8.43-8.46 (m, 2H), 7.48-7.52 (m, 3H), 7.19 (t, $J$ = 4.8 Hz, 1H).

**Experimental procedure for the preparation of 2-phenoxypyridine.[19]**

To an oven-dried 50 mL round bottomed flask, CuI (122.0 mg, 0.64 mmol, 0.1 equiv), picolinic acid (158 mg, 1.3 mmol, 0.2 equiv), phenol (715 mg, 7.6 mmol, 1.2 equiv) and $K_3PO_4$ (2.7 g, 12.8 mmol, 2.0 equiv) was added then the flask was evacuated and back-filled with $N_2$. To this reaction mixture, 2-bromopyridine (0.6 mL, 6.4 mmol, 1.0 equiv) and DMSO (12 mL) was added via syringe. The reaction mixture was stirred at 90 $^oC$ for 24 h under $N_2$. Then the reaction mixture was cooled to room temperature. The mixture was poured into water (30 mL) and extracted with ethyl acetate (30 mL). The organic layer was washed with water (20x2 mL) and brine (10 mL), dried over anhydrous $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by silica gel column chromatography using ethyl acetate/hexane as eluent to afford the desired product, 2-phenoxypyridine as a white solid. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 8.21 (dd, $J$ = 4.8 Hz, 1.2 Hz, 1H), 7.65-7.71 (m, 1H), 7.41 (t, $J$ = 7.8 Hz, 2H),

7.22 (d, *J* = 7.5 Hz, 1H), 7.15 (d, *J* = 7.8 Hz, 2H), 6.99 (dd, *J* = 5.1 Hz, 5.4 Hz, 1H), 6.91 (d, *J* = 8.4 Hz, 1H).

**Experimental procedure for the preparation of 1-phenyl-1*H*-pyrazole.[44]**

To a solution of $Cu(OAc)_2.H_2O$ (6.0 mg, 0.03 mmol, 0.01 equiv) in DMF (6.0 mL) were added iodobenzene (0.4 mL, 3.6 mmol, 1.2 equiv), 1*H*-pyrazole (204 mg, 3.0 mmol, 1.0 equiv), and $Cs_2CO_3$ (2.0 g, 6.0 mmol, 2.0 equiv) under $N_2$. The mixture was stirred at 110 $^oC$ for 24 h. Then the reaction mixture was cooled to room temperature. The mixture was poured into water (20 mL) and extracted with ethyl acetate (30 mL). The organic layer was washed with water (10x2 mL) and brine (10 mL), dried over anhydrous $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by silica gel column chromatography using ethyl acetate/hexane as eluent to afford the desired product, 1-phenyl-1*H*-pyrazole as colorless oil. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.94 (d, *J* = 2.1 Hz, 1H), 7.69-7.74 (m, 3H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.29 (t, *J* = 7.2 Hz, 1H), 6.48 (t, *J* = 1.8 Hz, 1H).

**Experimental procedure for the preparation of 2-phenylpyridine palladacycle dimer complex (11a).[36]**

To an oven-dried 50 mL round bottomed flask, 2-Phenylpyridine (155 mg, 1.0 mmol, 1.0 equiv) was added to a solution of $Pd(OAc)_2$ (225 mg, 1.0 mol, 1.0 equiv) in MeOH (16 mL) and stirred at room temperature for 6 h under $N_2$, during which time a yellow solid precipitated was formed in the solution. The precipitate was collected at the top of a plug of Celite, and the solids were washed with hexanes (3 x 10 mL). The yellow residue at the top of the celite plug was then washed through with $CH_2Cl_2$ (2 x 30 mL). The solvent was evaporated under reduced pressure, and the resulting solid was recrystallized from $CH_2Cl_2$/hexanes to afford the desired product as a yellow solid (82% yield). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.87 (d, *J* = 5.4 Hz, 2H), 7.38 (t, *J* = 7.8 Hz, 2H), 7.09 (d, *J* = 8.1 Hz, 2H), 6.79-6.94 (m, 8H), 6.45 (t, *J* = 6.6 Hz, 2H), 2.29 (s, 6H).

**General experimental procedure for the decarboxylative acylation reaction between 2-phenylpyridines and *α*-ketocarboxylic acids**, **Scheme 9**.

To an oven-dried 10 mL sealed tube, a mixture of 2-phenylpyridines (0.2 mmol, 1.0 equiv), *α*-ketocarboxylic acids (0.3-0.4 mmol, 1.5-2.0 equiv), potassium persulfate (108 mg, 0.4 mmol, 2.0 equiv) and palladium(II)acetate (4.6 mg, 0.02 mmol, 0.1 equiv) was taken and dry MeCN (3.0 mL) was added to it. After flushing with nitrogen for 30 seconds, immediately the vessel was sealed with a screw cap. The reaction mixture was allowed to stir for 16 h at room temperature. After that the reaction mixture was quenched with $NaHCO_3$ to remove the unreacted acids. Then the reaction mixture was poured into water (40 mL) and extracted with ethyl acetate (40 mL). The organic layer was washed with water (10 mL) and brine (10 mL), dried over anhydrous $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography using ethyl acetate/hexane as eluent to afford the desired product.

To note: During optimization, it was found that *α*-ketocarboxylic acids are hygroscopic in nature thus water or moisture is detrimental to the reaction outcome. Therefore, so after flushing with nitrogen the reaction vessel was immediately sealed with a screw cap.

**Phenyl(2-(pyridin-2-yl)phenyl)methanone, 7a, Scheme 9.**[7d] The same general procedure was followed by using 2-phenylpyridine (31.0 mg, 0.2 mmol, 1.0 equiv), 2-oxo-2-phenylacetic acid (45 mg, 0.3 mmol, 1.5 equiv), potassium persulfate (108 mg, 0.4 mmol, 2.0 equiv) and palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a white solid (39.5 mg, 76%), mp 105-107 $^oC$. $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 8.36 (d, $J$ = 4.2 Hz, 1H), 7.78 (d, $J$ = 7.8 Hz, 1H), 7.70 (d, $J$ = 7.8 Hz, 2H), 7.61 (t, $J$ = 7.2 Hz, 1H), 7.50-7.56 (m, 4H), 7.39 (t, $J$ = 7.2 Hz, 1H), 7.27 (t, $J$ = 7.2 Hz, 2H), 7.01 (t, $J$ = 4.8 Hz, 1H); $^{13}C$ NMR (150 MHz, $CDCl_3$): $\delta$ 198.2, 156.7, 149.0, 139.6, 139.5, 137.9, 136.3, 132.3, 130.2, 129.4, 129.1, 128.7, 128.5, 128.0, 122.6, 121.9; IR (neat): $\upsilon_{max}$ 1665, 1587, 1279, 929, 751, 703 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{18}H_{13}NO$ $[M]^+$: 259.0997; found: 259.0979.

**(2-(Pyridin-2-yl)phenyl)(*p*-tolyl)methanone, 7b, Scheme 9.**[7d] The same general procedure was followed by using 2-phenylpyridine (31.0 mg, 0.2 mmol, 1.0 equiv), 2-oxo-2-(*p*-tolyl)acetic acid (49 mg, 0.3 mmol, 1.5 equiv), potassium persulfate (108 mg,

0.4 mmol, 2.0 equiv) and palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a white solid (39.0 mg, 72%), mp 97-99 $^oC$. $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 8.41 (d, $J$ = 4.2 Hz, 1H), 7.78 (d, $J$ = 7.2 Hz, 1H), 7.56-7.62 (m, 4H), 7.52 (d, $J$ = 4.2 Hz, 2H), 7.49 (d, $J$ = 8.4 Hz, 1H), 7.09 (d, $J$ = 7.8 Hz, 2H), 7.03-7.06 (m, 1H), 2.33 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 197.9, 156.9, 149.1, 143.1, 139.7, 139.5, 136.2, 135.3, 130.0, 129.7, 128.92, 128.90, 128.8, 128.4, 122.8, 121.9, 21.6; IR (neat): $\upsilon_{max}$ 1662, 1604, 1433, 1284, 929, 751 $cm^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{19}H_{15}NONa$ $[M + Na]^+$: 296.1051; found: 296.1049.

**(4-(*tert*-Butyl)phenyl)(2-(pyridin-2-yl)phenyl)methanone, 7c, Scheme 9.**[45] The same general procedure was followed by using 2-phenylpyridine (31.0 mg, 0.2 mmol, 1.0 equiv), 2-(4-(*tert*-butyl)phenyl)-2-oxoacetic acid (62 mg, 0.3 mmol, 1.5 equiv), potassium persulfate (108 mg, 0.4 mmol, 2.0 equiv) and palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a yellowish oil (46.0 mg, 73%). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 8.40 (d, $J$ = 4.2 Hz, 1H), 7.76 (d, $J$ = 7.8 Hz, 1H), 7.65 (d, $J$ = 8.4 Hz, 2H), 7.46-7.62 (m, 5H), 7.30 (d, $J$ = 8.4 Hz, 2H), 7.00-7.04 (m, 1H), 1.27 (s, 9H); $^{13}C$ NMR (150 MHz, $CDCl_3$): $\delta$ 197.9, 157.0, 156.0, 149.1, 139.7, 139.6, 136.2, 135.1, 130.0, 129.6, 129.0, 128.9, 128.2, 125.0, 122.9, 121.8, 35.0, 31.0; IR (neat): $\upsilon_{max}$ 2961, 1666, 1598, 1466, 1277, 753 $cm^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{22}H_{21}NONa$ $[M + Na]^+$: 338.1521; found: 338.1523.

**(4-*iso*Butylphenyl)(2-(pyridin-2-yl)phenyl)methanone, 7d, Scheme 9.** The same general procedure was followed by using 2-phenylpyridine (31.0 mg, 0.2 mmol, 1.0 equiv), 2-(4-*iso*butylphenyl)-2-oxoacetic acid (62 mg, 0.3 mmol, 1.5 equiv), potassium persulfate (108 mg, 0.4 mmol, 2.0 equiv) and palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a colourless oil (45.0 mg, 71%). $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 8.39 (d, $J$ = 4.2 Hz, 1H), 7.76 (d, $J$ = 7.8 Hz, 1H), 7.51-7.62 (m, 6H), 7.45 (d, $J$ = 7.8 Hz, 1H), 7.03 (d, $J$ = 8.4 Hz, 2H), 7.00-7.02 (m, 1H), 2.43 (d, $J$ = 7.2 H, 2H), 1.78-1.85 (m,1H), 0.84 (d, $J$ = 6.6 Hz, 6H); $^{13}C$ NMR (150 MHz, $CDCl_3$): $\delta$ 198.0, 157.0,

149.0, 146.8, 139.7, 139.6, 136.1, 135.5, 130.1, 129.5, 129.1, 128.9, 128.7, 128.4, 123.0, 121.8, 45.3, 30.1, 22.2; IR (neat): $\upsilon_{max}$ 2957, 1664, 1602, 1281, 930, 751 $cm^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{22}H_{21}NONa$ $[M + Na]^+$: 338.1521; found: 338.1520.

**(4-Methoxyphenyl)(2-(pyridin-2-yl)phenyl)methanone, 7e, Scheme 9.**[7d] The same general procedure was followed by using 2-phenylpyridine (31.0 mg, 0.2 mmol, 1.0 equiv), 2-(4-methoxyphenyl)-2-oxoacetic acid (54 mg, 0.3 mmol, 1.5 equiv), potassium persulfate (108 mg, 0.4 mmol, 2.0 equiv) and palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a yellowish oil (35.0 mg, 60%). $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 8.44 (d, $J$ = 4.8 Hz, 1H), 7.78 (d, $J$ = 7.8 Hz, 1H), 7.68-7.70 (m, 2H), 7.56-7.62 (m, 2H), 7.52 (d, $J$ = 4.2 Hz, 2H), 7.48 (d, $J$ = 7.8 Hz, 1H), 7.05-7.07 (m, 1H), 6.76-6.79 (m,2H), 3.81 (s, 3H); $^{13}C$ NMR (150 MHz, $CDCl_3$): $\delta$ 197.0, 163.0, 157.0, 149.1, 139.6, 139.5, 136.2, 131.9, 130.7, 129.9, 129.0, 128.8, 128.3, 123.0, 121.9, 113.3, 55.3; IR (neat): $\upsilon_{max}$ 1658, 1597, 1464, 1256, 1027, 753 $cm^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{19}H_{15}NO_2Na$ $[M + Na]^+$: 312.1000; found: 312.0997.

**[1,1'-Biphenyl]-4-yl(2-(pyridin-2-yl)phenyl)methanone, 7f, Scheme 9.**[17] The same general procedure was followed by using 2-phenylpyridine (31.0 mg, 0.2 mmol, 1.0 equiv), 2-([1,1'-biphenyl]-4-yl)-2-oxoacetic acid (68 mg, 0.3 mmol, 1.5 equiv), potassium persulfate (108 mg, 0.4 mmol, 2.0 equiv) and palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a light yellow oil (55.0 mg, 82%). $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 8.41-8.42 (m, 1H), 7.78-7.82 (m, 3H), 7.64 (td, $J$ = 7.2 Hz, 1.2 Hz, 1H),7.52-7.61 (m, 8H), 7.45 (t, $J$ = 7.2, Hz, 2H), 7.38 (t, $J$ = 7.2 Hz, 1H), 7.03-7.05 (m, 1H); $^{13}C$ NMR (150 MHz, $CDCl_3$): $\delta$ 197.8, 156.8, 149.1, 144.9, 139.9, 139.6, 139.5, 136.6, 136.3, 130.2, 130.1, 129.0, 128.84, 128.82, 128.5, 128.0, 127.2, 126.7, 122.7, 122.0; IR (neat): $\upsilon_{max}$ 1662, 1595, 1280, 926, 745 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{24}H_{17}NO$ $[M]^+$: 335.1310; found: 335.1314.

**(4-Fluorophenyl)(2-(pyridin-2-yl)phenyl)methanone, 7g, Scheme 9.**[32b] The same general procedure was followed by using 2-phenylpyridine (31.0 mg, 0.2 mmol, 1.0 equiv), 2-(4-fluorophenyl)-2-oxoacetic acid (51.5 mg, 0.3 mmol, 1.5 equiv), potassium

persulfate (108 mg, 0.4 mmol, 2.0 equiv) and palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a yellowish oil (44.0 mg, 80%). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.38 (d, $J$ = 4.8 Hz, 1H), 7.78 (d, $J$ = 7.8 Hz, 1H), 7.70-7.73 (m, 2H), 7.59-7.65 (m, 2H), 7.54 (d, $J$ = 4.2 Hz, 2H), 7.52 (d, $J$ = 7.8 Hz, 1H), 7.04-7.06 (m, 1H), 6.92-6.96 (m, 2H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 196.7, 165.1 (d, $J$ = 252.0 Hz), 156.6, 149.0, 139.4, 139.2, 136.4, 134.3 (d, $J$ = 3.0 Hz), 131.9 (d, $J$ = 9.0 Hz), 130.3, 129.0, 128.7, 128.6, 122.6, 122.0, 115.1 (d, $J$ = 21.0 Hz); IR (neat): $\upsilon_{max}$ 1666, 1594, 1280, 1232, 1151, 752 cm$^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{18}H_{12}FNONa$ $[M + Na]^+$: 300.0801; found: 300.0806.

**(4-Chlorophenyl)(2-(pyridin-2-yl)phenyl)methanone, 7h, Scheme 9.**[7d] The same general procedure was followed by using 2-phenylpyridine (31.0 mg, 0.2 mmol, 1.0 equiv), 2-(4-chlorophenyl)-2-oxoacetic acid (55.5 mg, 0.3 mmol, 1.5 equiv), potassium persulfate (108 mg, 0.4 mmol, 2.0 equiv) and palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a yellowish oil (37.5 mg, 64%). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.35-8.36 (m, 1H), 7.79 (d, $J$ = 7.8 Hz, 1H), 7.60-7.64 (m, 4H), 7.52-7.56 (m, 3H), 7.24-7.28 (m, 2H), 7.05-7.07 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 197.0, 156.4, 149.0, 139.4, 139.1, 138.6, 136.45, 136.41, 130.7, 130.3, 129.0, 128.6, 128.3, 122.4, 122.1; IR (neat): $\upsilon_{max}$ 2925, 1669, 1587, 1280, 1089, 928, 750 cm$^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{18}H_{12}ClNONa$ $[M + Na]^+$: 316.0505; found: 316.0503.

**(4-Bromophenyl)(2-(pyridin-2-yl)phenyl)methanone, 7i, Scheme 9.**[32b] The same general procedure was followed by using 2-phenylpyridine (31.0 mg, 0.2 mmol, 1.0 equiv), 2-(4-bromophenyl)-2-oxoacetic acid (69 mg, 0.3 mmol, 1.5 equiv), potassium persulfate (108 mg, 0.4 mmol, 2.0 equiv) and palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a yellowish solid (54.5 mg, 81%), mp 102-104 $^o$C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.35-8.36 (m, 1H), 7.78 (d, $J$ = 7.8 Hz, 1H), 7.60-7.64 (m, 2H), 7.52-7.57 (m, 5H), 7.40-7.42 (m, 2H), 7.05-7.07 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 196.9, 156.4, 148.9, 139.4, 139.0, 136.8, 136.5, 131.3, 130.8, 130.3, 129.0,

128.64, 128.58, 127.2, 122.4, 122.1; IR (neat): $\upsilon_{max}$ 1670, 1584, 1279, 1067, 927, 750 $cm^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{18}H_{12}BrNONa$ $[M + Na]^+$: 360.0000; found: 360.0002.

**(2-(Pyridin-2-yl)phenyl)(4-(trifluoromethyl)phenyl)methanone, 7j, Scheme 9.[17]** The same general procedure was followed by using 2-phenylpyridine (31.0 mg, 0.2 mmol, 1.0 equiv), 2-oxo-2-(4-(trifluoromethyl)phenyl)acetic acid (65.5 mg, 0.3 mmol, 1.5 equiv), potassium persulfate (108 mg, 0.4 mmol, 2.0 equiv) and palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a white solid (37.0 mg, 57%), mp 76-78 $^oC$. $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 8.30-8.31 (m, 1H), 7.78-7.81 (m, 3H), 7.54-7.66 (m, 5H), 7.53 (d, *J* = 7.8 Hz, 2H), 7.02-7.04 (m, 1H); $^{13}C$ NMR (150 MHz, $CDCl_3$): $\delta$ 196.9, 156.0, 148.8, 141.0, 139.4, 138.8, 136.6, 133.2 (q, *J* = 31.5 Hz), 130.5, 129.3, 129.1, 128.8, 128.4, 125.0 (q, *J* = 3.0 Hz), 123.6 (q, *J* = 271.5 Hz), 122.2, 122.1; IR (neat): $\upsilon_{max}$ 1675, 1587, 1322, 1130, 753 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{19}H_{12}F_3NO$ $[M]^+$: 327.0871; found: 327.0867.

**Naphthalen-1-yl(2-(pyridin-2-yl)phenyl)methanone, 7k, Scheme 9.[32b]** The same general procedure was followed by using 2-phenylpyridine (31.0 mg, 0.2 mmol, 1.0 equiv), 2-(naphthalen-1-yl)-2-oxoacetic acid (60 mg, 0.3 mmol, 1.5 equiv), potassium persulfate (108 mg, 0.4 mmol, 2.0 equiv) and palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a yellowish solid (34.5 mg, 56%), mp 101-103 $^oC$. $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 8.93 (d, *J* = 8.4 Hz, 1H), 8.14 (d, *J* = 4.8 Hz, 1H), 7.75-7.78 (m, 3H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.63-7.66 (m, 2H), 7.56 (td, *J* = 7.8 Hz, 1.2 Hz, 1H), 7.52 (t, *J* = 7.2 Hz, 1H), 7.35-7.43 (m, 3H), 7.17 (t, *J* = 7.8 Hz, 1H), 6.76-6.78 (m, 1H); $^{13}C$ NMR (150 MHz, $CDCl_3$): $\delta$ 199.6, 157.0, 148.9, 141.0, 140.2, 136.3, 136.0, 133.5, 132.3, 131.0, 130.6, 130.1, 129.6, 128.8, 128.5, 128.0, 127.6, 126.5, 126.2, 123.7, 122.2, 121.4; IR (neat): $\upsilon_{max}$ 1662, 1586, 1432, 1279, 750 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{22}H_{15}NO$ $[M]^+$: 309.1154; found: 309.1133.

**(2-Bromophenyl)(2-(pyridin-2-yl)phenyl)methanone, 7l, Scheme 9.[46]** The same general procedure was followed by using 2-phenylpyridine (31.0 mg, 0.2 mmol, 1.0 equiv), 2-(2-bromophenyl)-2-oxoacetic acid (69 mg, 0.3 mmol, 1.5 equiv), potassium

persulfate (108 mg, 0.4 mmol, 2.0 equiv) and palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a yellowish oil (54.0 mg, 80%). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.52-8.54 (m, 1H), 7.70-7.71 (m, 1H), 7.61-7.66 (m, 2H), 7.57 (td, $J$ = 7.8 Hz, 1.8 Hz, 1H), 7.53 (td, $J$ = 7.2 Hz, 1.2 Hz, 1H), 7.44-7.46 (m, 2H), 7.23-7.26 (m, 1H), 7.06-7.09 (m, 2H), 7.01-7.03 (m, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 196.7, 157.1, 149.1, 140.7, 139.4, 138.7, 136.2, 139.9, 131.6, 131.3, 131.2, 130.6, 129.3, 128.6, 126.5, 122.8, 121.8, 121.4; IR (neat): $\upsilon_{max}$ 1673, 1586, 1464, 1432, 1292, 928, 750 cm$^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{18}H_{12}BrNO$ $[M]^+$: 337.0102; found: 337.0101.

**(2,4-Dimethylphenyl)(2-(pyridin-2-yl)phenyl)methanone, 7m, Scheme 9.** The same general procedure was followed by using 2-phenylpyridine (31.0 mg, 0.2 mmol, 1.0 equiv), 2-(2,4-dimethylphenyl)-2-oxoacetic acid (53.5 mg, 0.3 mmol, 1.5 equiv), potassium persulfate (108 mg, 0.4 mmol, 2.0 equiv) and palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a light yellow oil (40.0 mg, 70%). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.46-8.47 (m, 1H), 7.66-7.67 (m, 1H), 7.56-7.60 (m, 3H), 7.49-7.52 (m, 1H), 7.42 (d, $J$ = 7.8 Hz, 1H), 7.11 (d, $J$ = 8.4 Hz, 1H), 7.03-7.05 (m, 1H), 6.92 (s, 1H), 6.76 (d, $J$ = 7.8 Hz, 1H), 2.56 (s, 3H), 2.24 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 199.5, 157.4, 148.7, 141.5, 141.0, 139.8, 139.4, 136.3, 135.2, 132.1, 131.2, 130.3, 129.6, 129.2, 128.4, 125.5, 122.8, 121.8, 21.3, 21.0; IR (neat): $\upsilon_{max}$ 2924, 1663, 1601, 1436, 1299, 753 cm$^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{20}H_{17}NO$ $[M]^+$: 287.1310; found: 287.1305.

**(3,5-Dimethoxyphenyl)(2-(pyridin-2-yl)phenyl)methanone, 7n, Scheme 9.** The same general procedure was followed by using 2-phenylpyridine (31.0 mg, 0.2 mmol, 1.0 equiv), 2-(3,5-dimethoxyphenyl)-2-oxoacetic acid (63 mg, 0.3 mmol, 1.5 equiv), potassium persulfate (108 mg, 0.4 mmol, 2.0 equiv) and palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a colourless oil (37.0 mg, 58%). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.40 (d, $J$ = 4.8 Hz, 1H), 7.77 (d, $J$ = 7.8 Hz, 1H), 7.58-7.61 (m, 2H), 7.50-7.54 (m, 3H), 7.04-7.06 (m, 1H), 6.96 (d, $J$ = 1.8 Hz, 2H), 6.50 (t, $J$ = 2.4 Hz, 1H), 3.73 (s, 6H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 197.6, 160.3, 156.7, 149.0, 139.8, 139.5,

139.3, 136.3, 130.2, 129.1, 128.7, 128.4, 122.4, 122.0, 107.3, 105.0, 55.5; IR (neat): $\upsilon_{max}$ 1670, 1594, 1462, 1302, 1156, 1062, 753 $cm^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{20}H_{17}NO_3Na$ $[M + Na]^+$: 342.1106; found: 342.1007.

**(5-Methyl-2-(pyridin-2-yl)phenyl)(phenyl)methanone, 7o, Scheme 9.**[37d] The same general procedure was followed by using 2-(*p*-tolyl)pyridine (34.0 mg, 0.2 mmol, 1.0 equiv), 2-oxo-2-phenylacetic acid (60 mg, 0.4 mmol, 2.0 equiv), potassium persulfate (108 mg, 0.4 mmol, 2.0 equiv) and palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a white solid (40.0 mg, 73%), mp 137-139 $^oC$. $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 8.35 (d, *J* = 4.8 Hz, 1H), 7.68-7.70 (m, 3 H), 7.55 (td, *J* = 7.8 Hz, 1.8 Hz, 1H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.42 (d, *J* = 7.8 Hz, 1H), 7.36-7.40 (m, 2H), 7.26-7.28 (m, 2H), 6.98-7.00 (m, 1H), 2.47 (s, 3H); $^{13}C$ NMR (150 MHz, $CDCl_3$): $\delta$ 198.4, 156.6, 148.9, 139.4, 138.6, 137.9, 136.8, 136.2, 132.2, 130.9, 129.6, 129.4, 128.5, 127.9, 122.4, 121.6, 21.2; IR (neat): $\upsilon_{max}$ 1666, 1588, 1461, 1250, 698 $cm^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{19}H_{15}NONa$ $[M + Na]^+$: 296.1051; found: 296.1051.

**(5-(*tert*-Butyl)-2-(pyridin-2-yl)phenyl)(phenyl)methanone, 7p, Scheme 9.**[45] The same general procedure was followed by using 2-(4-(*tert*-butyl)phenyl)pyridine (42.5 mg, 0.2 mmol, 1.0 equiv), 2-oxo-2-phenylacetic acid (60 mg, 0.4 mmol, 2.0 equiv), potassium persulfate (108 mg, 0.4 mmol, 2.0 equiv) and palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a yellowish oil (38.0 mg, 60%). $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 8.35 (d, *J* = 4.2 Hz, 1H), 7.70-7.73 (m, 3H), 7.64 (dd, *J* = 7.8 Hz, 1.8 Hz, 1H), 7.53-7.56 (m, 2H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.38 (t, *J* = 7.2 Hz, 1H), 7.26-7.28 (m, 2H), 6.98-7.00 (m, 1H), 1.39 (s, 9H); $^{13}C$ NMR (150 MHz, $CDCl_3$): $\delta$ 198.7, 156.7, 151.8, 148.9, 139.0, 138.0, 136.8, 136.2, 132.2, 129.4, 128.4, 127.9, 127.3, 126.0, 122.4, 121.6, 34.8, 31.2; IR (neat): $\upsilon_{max}$ 2962, 1667, 1590, 1467, 1249, 751 $cm^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{22}H_{21}NONa$ $[M + Na]^+$: 338.1521; found: 338.1521.

**(4-Methyl-2-(pyridin-2-yl)phenyl)(phenyl)methanone, 7q, Scheme 9.**[32b] The same general procedure was followed by using 2-(*m*-tolyl)pyridine (34.0 mg, 0.2 mmol, 1.0 equiv), 2-oxo-2-phenylacetic acid (60 mg, 0.4 mmol, 2.0 equiv), potassium persulfate

(108 mg, 0.4 mmol, 2.0 equiv) and palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a white solid (38.0 mg, 70%), mp 106-108 $^oC$. $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 8.40 (d, $J$ = 4.2 Hz, 1H), 7.68 (d, $J$ = 7.2 Hz, 2H), 7.58 (s, 1H), 7.52-7.55 (m, 1H), 7.47 (d, $J$ = 7.8 Hz, 1H), 7.44 (d, $J$ = 7.8 Hz, 1H), 7.38 (t, $J$ = 7.2 Hz, 1H), 7.34 (d, $J$ = 7.8 Hz, 1H), 7.24-7.28 (m, 2H), 7.00-7.02 (m, 1H), 2.51 (s, 3H); $^{13}C$ NMR (150 MHz, $CDCl_3$): $\delta$ 198.2, 157.1, 149.0, 140.6, 139.9, 138.0, 136.6, 136.1, 132.2, 129.6, 129.5, 129.4, 129.1, 127.9, 123.0, 121.8, 21.5; IR (neat): $\upsilon_{max}$ 1665, 1588, 1281, 932, 702 $cm^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{19}H_{15}NONa$ $[M + Na]^+$: 296.1051; found: 296.1050.

**(2-(Pyridin-2-yl)phenyl)(*m*-tolyl)methanone, 7r, Scheme 9.**[47] The same general procedure was followed by using 2-phenylpyridine (31.0 mg, 0.2 mmol, 1.0 equiv), 2-oxo-2-(*m*-tolyl)acetic acid (49 mg, 0.3 mmol, 1.5 equiv), potassium persulfate (108 mg, 0.4 mmol, 2.0 equiv) and palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a yellowish oil (38.0 mg, 70%). $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 8.39 (d, $J$ = 4.8 Hz, 1H), 7.77 (d, $J$ = 7.8 Hz, 1H), 7.61 (td, $J$ = 7.2 Hz, 2.4 Hz, 1H), 7.48-7.58 (m, 6H), 7.22 (d, $J$ = 7.2 Hz, 1H), 7.16 (t, $J$ = 7.8 Hz, 1H), 7.02-7.04 (m, 1H), 2.29 (s, 3H); $^{13}C$ NMR (150 MHz, $CDCl_3$): $\delta$ 198.4, 156.9, 149.0, 139.7, 139.6, 137.7, 136.2, 133.2, 130.1, 129.9, 129.1, 128.8,128.4, 127.9, 127.0, 122.7, 121.9, 21.2; IR (neat): $\upsilon_{max}$ 1666, 1588, 1432, 1284, 752 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{19}H_{15}NO$ $[M]^+$: 273.1154; found: 273.1150.

**(5-Methoxy-2-(pyridin-2-yl)phenyl)(m-tolyl)methanone, 7s, Scheme 9**. The same general procedure was followed by using 2-(4-methoxyphenyl)pyridine (37.0 mg, 0.2 mmol, 1.0 equiv), 2-oxo-2-(m-tolyl)acetic acid (66 mg, 0.4 mmol, 2.0 equiv), potassium persulfate (108 mg, 0.4 mmol, 2.0 equiv) and palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a yellowish oil (42.5 mg, 70%). $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 8.34 (d, $J$ = 4.8 Hz, 1H), 7.72 (d, $J$ = 8.4 Hz, 1H), 7.55 (s, 1H), 7.51-7.54 (m, 1H), 7.48 (d, $J$ = 7.2 Hz, 1H), 7.44 (d, $J$ = 7.8 Hz, 1H), 7.20 (d, $J$ = 7.8 Hz, 1H), 7.12-7.16 (m, 2H), 7.05 (d, $J$ = 2.4 Hz, 1H), 6.96-6.98 (m, 1H), 3.88 (s, 3H), 2.28 (s, 3H); $^{13}C$

NMR (150 MHz, $CDCl_3$): $\delta$ 198.1, 159.7, 156.4, 148.8, 140.8, 137.7, 137.6, 136.1, 133.2, 132.0, 130.0, 129.8, 127.9, 126.8, 122.1, 121.3, 116.0, 114.0, 55.5, 21.2; IR (neat): $\upsilon_{max}$ 1667, 1595, 1464, 1288, 1234, 753 $cm^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{20}H_{17}NO_2Na$ $[M + Na]^+$: 326.1157; found: 326.1161.

**(5-Methoxy-2-(pyridin-2-yl)phenyl)(phenyl)methanone, 7t, Scheme 9.**[32b] The same general procedure was followed by using 2-(4-methoxyphenyl)pyridine (37.0 mg, 0.2 mmol, 1.0 equiv), 2-oxo-2-phenylacetic acid (60 mg, 0.4 mmol, 2.0 equiv), potassium persulfate (108 mg, 0.4 mmol, 2.0 equiv) and palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a white solid (46.0 mg, 80%). mp 98-100 $^oC$. $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 8.32 (d, *J* = 4.8 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.70 (d, *J* = 7.2 Hz, 2H), 7.53 (td, *J* = 7.8 Hz, 1.2 Hz, 1H), 7.45 (d, *J* = 7.8 Hz, 1H), 7.38 (t, *J* = 7.2 Hz, 1H), 7.26-7.28 (m, 2H), 7.14 (dd, *J* = 8.4 Hz, 2.4 Hz, 1H), 7.06 (d, *J* = 2.4 Hz, 1H), 6.95-6.97 (m, 1H), 3.89 (s, 3H); $^{13}C$ NMR (150 MHz, $CDCl_3$): $\delta$ 197.9, 159.8, 156.3, 148.8, 140.8, 137.7, 136.2, 132.3, 132.0, 129.9, 129.3, 128.0, 122.0, 121.3, 116.1, 114.0, 55.6; IR (neat): $\upsilon_{max}$ 1666, 1595, 1462, 1286, 1230, 741, 700 $cm^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{19}H_{15}NO_2Na$ $[M + Na]^+$: 312.1000; found: 312.1003.

**(4-Fluorophenyl)(5-methoxy-2-(pyridin-2 yl)phenyl)methanone, 7u, Scheme 9.** The same general procedure was followed by using 2-(4-methoxyphenyl)pyridine (37.0 mg, 0.2 mmol, 1.0 equiv), 2-(4-fluorophenyl)-2-oxoacetic acid (67 mg, 0.4 mmol, 2.0 equiv), potassium persulfate (108 mg, 0.4 mmol, 2.0 equiv) and palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a white solid (39.0 mg, 64%), mp 74-76 $^oC$. $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 8.31 (d, *J* = 4.8 Hz, 1H), 7.70-7.73 (m, 3H), 7.55 (td, *J* = 7.8 Hz, 1.8 Hz, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.14 (dd, *J* = 8.4 Hz, 2.4 Hz, 1H), 7.4 (d, *J* = 2.4 Hz, 1H), 6.98 (dd, *J* = 7.2 Hz, 4.8 Hz,1H), 6.93 (t, *J* = 8.4 Hz, 2H), 3.89 (s, 3H); $^{13}C$ NMR (150 MHz, $CDCl_3$): $\delta$ 196.3, 165.1 (d, *J* = 252.0 Hz), 159.9, 156.1, 148.8, 140.5, 136.3, 134.2 (d, *J* = 3.0 Hz), 131.8 (d, *J* = 9.0 Hz), 129.9, 121.9, 121.4, 116.1, 115.1 (d, *J* = 21.0 Hz), 113.9, 55.6; IR (neat): $\upsilon_{max}$ 1668, 1596, 1464, 1289, 1230, 850 $cm^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{19}H_{14}FNO_2Na$ $[M + Na]^+$: 330.0906; found: 330.0872.

**(4-Bromophenyl)(5-methoxy-2-(pyridin-2-yl)phenyl)methanone, 7v, Scheme 9.** The same general procedure was followed by using 2-(4-methoxyphenyl)pyridine (37.0 mg, 0.2 mmol, 1.0 equiv), 2-(4-bromophenyl)-2-oxoacetic acid (92 mg, 0.4 mmol, 2.0 equiv), potassium persulfate (108 mg, 0.4 mmol, 2.0 equiv) and palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a yellowish solid (49.0 mg, 67%), mp 107-109 $^oC$. $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 8.28 (d, $J$ = 4.8 Hz, 1H), 7.72 (d, $J$ = 8.4 Hz, 1H), 7.55-7.57 (m, 3H), 7.48 (d, $J$ = 7.8 Hz, 1H), 7.39 (d, $J$ = 9.0 Hz, 2H), 7.13 (dd, $J$ = 9.0 Hz, 3.0 Hz, 1H), 7.03 (d, $J$ = 3.0 Hz, 1H), 6.98 (dd, $J$ = 7.2 Hz, 4.8 Hz, 1H), 3.88 (s, 3H); $^{13}C$ NMR (150 MHz, $CDCl_3$): $\delta$ 196.8, 159.9, 155.8, 148.7, 140.3, 136.7, 136.4, 131.7, 131.3, 130.7, 129.8, 127.2, 121.7, 121.5, 116.2, 113.9, 55.6; IR (neat): $\upsilon_{max}$ 1669, 1586, 1464, 1230, 841, 757 $cm^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{19}H_{14}BrNO_2Na$ $[M + Na]^+$: 390.0106; found: 390.0104.

**3-Methyl-1-(2-(pyridin-2-yl)phenyl)butan-1-one, 7w, Scheme 9.**[17] The same general procedure was followed by using 2-phenylpyridine (31.0 mg, 0.2 mmol, 1.0 equiv), 4-methyl-2-oxopentanoic acid (52 mg, 0.4 mmol, 2.0 equiv), potassium persulfate (108 mg, 0.4 mmol, 2.0 equiv) and palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a colourless oil (34.0 mg, 71%). $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 8.62 (d, $J$ = 4.2 Hz, 1H), 7.76 (td, $J$ = 7.8 Hz, 1.8 Hz, 1H), 7.61 (d, $J$ = 7.2 Hz, 1H), 7.56 (d, $J$ = 8.4 Hz, 1H), 7.44-7.52 (m, 3H), 7.24-7.28 (m, 1H), 2.40 (d, $J$ = 6.6 Hz, 2H), 2.09-2.16 (m, 1H), 0.87 (d, $J$ = 7.2 Hz, 6H); $^{13}C$ NMR (150 MHz, $CDCl_3$): $\delta$ 206.6, 157.6, 149.2, 142.0, 138.6, 136.7, 130.0, 129.2, 128.5, 127.5, 122.6, 122.2, 51.7, 24.8, 22.6; IR (neat): $\upsilon_{max}$ 2956, 1693, 1587, 1465, 1208, 754 $cm^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{16}H_{17}NONa$ $[M + Na]^+$: 262.1208; found: 262.1207.

**Phenyl(2-(pyrimidin-2-yl)phenyl)methanone, 7x, Scheme 9.**[48] The same general procedure was followed by using 2-phenylpyrimidine (31.5 mg, 0.2 mmol, 1.0 equiv), 2-oxo-2-phenylacetic acid (45 mg, 0.4 mmol, 1.5 equiv), potassium persulfate (108 mg, 0.4 mmol, 2.0 equiv) and palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired

product as a white solid (33 mg, 63%), mp 129-131 $^{o}$C. $^{1}$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.56 (d, *J* = 4.8 Hz, 2H), 8.38 (d, J = 7.2 Hz, 1H), 7.73 (d, *J* = 7.2 Hz, 2H), 7.66 (t, *J* = 7.8 Hz, 1H), 7.61 (t, *J* = 7.8 Hz, 1H), 7.52 (d, *J* = 7.2 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 1H), 7.30 (t, *J* = 7.8 Hz, 2H), 7.00 (t, *J* = 4.8 Hz, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 197.8, 163.9, 156.6, 140.5, 138.1, 136.9, 132.2, 130.3, 129.9, 129.4, 129.0, 128.6, 128.1, 118.7; IR (neat): $\upsilon_{max}$ 1664, 1557, 1413, 1281, 752 cm$^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{17}H_{12}N_2ONa$ $[M + Na]^+$: 283.0847; found: 283.0841.

**Decarboxylative acylation reaction in gram scale (Synthesis of phenyl(2-(pyridin-2-yl)phenyl)methanone, 7a, Scheme 9).**

To an oven-dried 100 mL sealed tube, a mixture of 2-phenylpyridines (0.93 mL, 6.5 mmol, 1.0 equiv), 2-oxo-2-phenylacetic acid (1.46g, 9.8 mmol, 1.5 equiv), potassium persulfate (3.51g, 13.0 mmol, 2.0 equiv) and palladium(II)acetate (146 mg, 0.65 mmol, 0.1 equiv) was taken and dry MeCN (50 mL) was added to it. After flushing with nitrogen for 30 seconds, immediately the vessel was sealed with a screw cap. The reaction mixture was allowed to stir for 16 h at room temperature. After that the reaction mixture was quenched with $NaHCO_3$ to remove the unreacted acids. Then the reaction mixture was poured into water (80 mL) and extracted with ethyl acetate (60x2 mL). The organic layer was washed with water (30x2 mL) and brine (30 mL), dried over anhydrous $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The pure phenyl(2-(pyridin-2-yl)phenyl)methanone (**7a**) was obtained as a white solid in 68% (1.15 g) yield after column chromatography of the crude reaction mixture using ethyl acetate/hexane (7:3) as eluent.

**General experimental procedure for the decarbonylative acylation reaction between 2-phenylpyridines and phenylglyoxals**, **Scheme 10**.

To an oven-dried 10 mL sealed tube, a mixture of 2-phenylpyridines (0.2 mmol, 1.0 equiv), phenylglyoxals (0.3 mmol, 1.5 equiv), potassium persulfate (108 mg, 0.4 mmol, 2.0 equiv) and palladium(II)acetate (4.6 mg, 0.02 mmol, 0.1 equiv) was taken and dry MeCN (3.0 mL) was added to it. After flushing with nitrogen, immediately the vessel was sealed with a screw cap. The reaction mixture was allowed to stir for 16 h at room

temperature. After that the reaction mixture was quenched with $NaHCO_3$. Then the reaction mixture was poured into water (40 mL) and extracted with ethyl acetate (40 mL). The organic layer was washed with water (10 mL) and brine (10 mL), dried over anhydrous $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography using ethyl acetate/hexane as eluent to afford the desired product.

**Phenyl(2-(pyridin-2-yl)phenyl)methanone, 7a, Scheme 10.** The same general procedure was followed by using 2-phenylpyridine (31.0 mg, 0.2 mmol, 1.0 equiv), 2-oxo-2-phenylacetaldehyde (40 mg, 0.3 mmol, 1.5 equiv), potassium persulfate (108 mg, 0.4 mmol, 2.0 equiv) and palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a white solid (36.5 mg, 70%), mp 105-107 $^oC$. The spectral data of compound **7a** is in decarboxylative acylation part.

**(2-(Pyridin-2-yl)phenyl)(*p*-tolyl)methanone, 7b, Scheme 10.** The same general procedure was followed by using 2-phenylpyridine (31.0 mg, 0.2 mmol, 1.0 equiv), 2-oxo-2-(*p*-tolyl)acetaldehyde (45 mg, 0.3 mmol, 1.5 equiv), potassium persulfate (108 mg, 0.4 mmol, 2.0 equiv) and palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a white solid (26 mg, 48%), mp 97-99 $^oC$. The spectral data of compound **7b** is in decarboxylative acylation part.

**(4-Fluorophenyl)(2-(pyridin-2-yl)phenyl)methanone, 7g, Scheme 10.** The same general procedure was followed by using 2-phenylpyridine (31.0 mg, 0.2 mmol, 1.0 equiv), 2-(4-fluorophenyl)-2-oxoacetaldehyde (46 mg, 0.3 mmol, 1.5 equiv), potassium persulfate (108 mg, 0.4 mmol, 2.0 equiv) and palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a yellowish oil (31.0 mg, 56%). The spectral data of compound **7g** is in decarboxylative acylation part.

**(4-Chlorophenyl)(2-(pyridin-2-yl)phenyl)methanone, 7h, Scheme 10.** The same general procedure was followed by using 2-phenylpyridine (31.0 mg, 0.2 mmol, 1.0

equiv), 2-(4-chlorophenyl)-2-oxoacetaldehyde (51.0 mg, 0.3 mmol, 1.5 equiv), potassium persulfate (108 mg, 0.4 mmol, 2.0 equiv) and palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a yellowish oil (33.5 mg, 57%). The spectral data of compound **7h** is in decarboxylative acylation part.

**(2-Bromophenyl)(2-(pyridin-2-yl)phenyl)methanone, 7l, Scheme 10.** The same general procedure was followed by using 2-phenylpyridine (31.0 mg, 0.2 mmol, 1.0 equiv), 2-(2-bromophenyl)-2-oxoacetaldehyde (64.0 mg, 0.3 mmol, 1.5 equiv), potassium persulfate (108 mg, 0.4 mmol, 2.0 equiv) and palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a yellowish oil (40.5 mg, 60%). The spectral data of compound **7l** is in Scheme 9.

**(2-(Pyridin-2-yl)phenyl)(m-tolyl)methanone, 7r, Scheme 10.** The same general procedure was followed by using 2-phenylpyridine (31.0 mg, 0.2 mmol, 1.0 equiv), 2-oxo-2-(*m*-tolyl)acetaldehyde (45 mg, 0.3 mmol, 1.5 equiv), potassium persulfate (108 mg, 0.4 mmol, 2.0 equiv) and palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a yellowish oil (26.0 mg, 47%). The spectral data of compound **7r** is in Scheme 9.

**(5-fluoro-2-(pyridin-2-yl)phenyl)(phenyl)methanone, 7y, Scheme 10.**[32b] The same general procedure was followed by using 2-(4-fluorophenyl)pyridine (35.0 mg, 0.2 mmol, 1.0 equiv), 2-oxo-2-phenylacetaldehyde (40 mg, 0.3 mmol, 1.5 equiv), potassium persulfate (108 mg, 0.4 mmol, 2.0 equiv) and palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a white solid (26.5 mg, 48%), mp 149-151 $^{o}$C. $^{1}$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.36 (d, $J$ = 4.8 Hz, 1H), 7.78 (dd, $J$ = 8.4 Hz, 4.8 Hz, 1H), 7.69 (d, $J$ = 7.8 Hz, 2H), 7.58 (td, $J$ = 7.8 Hz, 1.2 Hz, 1H), 7.48 (d, $J$ = 7.8 Hz, 1H), 7.42 (t, $J$ = 7.2 Hz, 1H), 7.25-7.33 (m, 4H), 7.03 (dd, $J$ = 6.6 Hz, 5.4 Hz, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 196.4, 162.6 (d, $J$ = 249.0 Hz), 155.6, 148.9, 141.4 (d, $J$ = 4.5 Hz), 137.2, 136.5, 135.5 (d, $J$ = 1.5 Hz), 132.6, 130.6 (d, $J$ = 7.5 Hz), 129.3, 128.1, 122.4, 122.0,

117.1 (d, *J* = 21.0 Hz), 116.1 (d, *J* = 22.5 Hz); IR (neat): $\upsilon_{max}$ 1661, 1588, 1279, 846, 789 $cm^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{18}H_{12}FNONa$ $[M + Na]^+$: 300.0801; found: 300.0802.

**(5-chloro-2-(pyridin-2-yl)phenyl)(phenyl)methanone, 7z, Scheme 10.**[17] The same general procedure was followed by using 2-(4-chlorophenyl)pyridine (38.0 mg, 0.2 mmol, 1.0 equiv), 2-oxo-2-phenylacetaldehyde (40 mg, 0.3 mmol, 1.5 equiv), potassium persulfate (108 mg, 0.4 mmol, 2.0 equiv) and palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a white solid (33.0 mg, 56%), mp 113-115 $^oC$. $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 8.36 (d, *J* = 4.2 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.69 (dd, *J* = 8.4 Hz, 1.2 Hz, 2H), 7.57-7.61 (m, 2H), 7.52 (d, *J* = 1.8 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.40-7.43 (m, 1H), 7.30 (t, *J* = 7.8 Hz, 2H), 7.04-7.06 (m, 1H); $^{13}C$ NMR (150 MHz, $CDCl_3$): $\delta$ 195.8, 155.4, 148.9, 141.0, 137.7, 137.2, 136.6, 134.9, 132.6, 130.2, 129.9, 129.3, 129.0, 128.2, 122.4, 122.2; IR (neat): $\upsilon_{max}$ 1688, 1588, 1458, 1276, 786 $cm^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{18}H_{12}ClNONa$ $[M + Na]^+$: 316.0505; found: 316.0502.

**(5-bromo-2-(pyridin-2-yl)phenyl)(phenyl)methanone, 7aa, Scheme 10.**[35a] The same general procedure was followed by using 2-(4-bromophenyl)pyridine (47.0 mg, 0.2 mmol, 1.0 equiv), 2-oxo-2-phenylacetaldehyde (40 mg, 0.3 mmol, 1.5 equiv), potassium persulfate (108 mg, 0.4 mmol, 2.0 equiv) and palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a white solid (28.5 mg, 42%), mp 109-111 $^oC$. $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 8.36 (d, *J* = 4.2 Hz, 1H), 7.74 (dd, *J* = 7.8 Hz, 1.8 Hz, 1H), 7.66-7.69 (m, 4H), 7.59 (td, *J* = 7.8 Hz, 1.8 Hz, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.42 (t, *J* = 7.2 Hz, 1H), 7.30 (t, *J* = 7.8 Hz, 2H), 7.04 (dd, *J* = 6.6 Hz, 4.8 Hz, 1H); $^{13}C$ NMR (150 MHz, $CDCl_3$): $\delta$ 196.2, 155.5, 149.0, 141.1, 138.2, 137.2, 136.6, 133.1, 132.6, 131.8, 130.1, 129.4, 128.2, 123.0, 122.4, 122.3; IR (neat): $\upsilon_{max}$ 1668, 1587, 1458, 1275, 786 $cm^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{18}H_{12}BrNONa$ $[M + Na]^+$: 360.0000, 361.9979; found: 359.9971, 361.9979.

**(3-methyl-2-(pyridin-2-yl)phenyl)(phenyl)methanone, 7ab, Scheme 10.**[32b] The same general procedure was followed by using 2-(*o*-tolyl)pyridine (34.0 mg, 0.2 mmol, 1.0 equiv), 2-oxo-2-phenylacetaldehyde (40 mg, 0.3 mmol, 1.5 equiv), potassium persulfate

(108 mg, 0.4 mmol, 2.0 equiv) and palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a colourless oil (27.0 mg, 50%). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.49 (d, $J$ = 4.2 Hz, 1H), 7.65 (d, $J$ = 7.2 Hz, 2H), 7.60 (t, $J$ = 7.2 Hz, 1H), 7.46 (d, $J$ = 7.2 Hz, 1H), 7.40-7.43 (m, 2H), 7.37 (d, $J$ = 7.2 Hz, 1H), 7.28-7.31 (m, 3H), 7.08 (dd, $J$ = 6.6 Hz, 5.4 Hz, 1H), 2.30 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 198.2, 157.3, 148.7, 140.0, 137.6, 136.8, 136.1, 132.6, 132.5, 129.9, 129.8, 128.0, 127.9, 126.2, 125.3, 121.9, 20.1; IR (neat): $\upsilon_{max}$ 1666, 1589, 1282, 752, 707 cm$^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{19}H_{15}NONa$ $[M + Na]^+$: 296.1051; found: 296.1062.

**General experimental procedure for the dehydrogenative acylation reaction between 2-phenylpyridines and aldehydes**, **Scheme 11**.

To an oven-dried 7 mL clear vial, a mixture of 2-phenylpyridines (0.2 mmol, 1.0 equiv) and palladium(II)acetate (4.6 mg, 0.02 mmol, 0.1 equiv) was taken and dry MeCN (3.0 mL) was added to it. The corresponding aldehydes (0.3 mmol 1.5 equiv) were added to the reaction mixture. After flushing with nitrogen for 30 seconds, immediately the vessel was sealed with a screw cap. Then aq. TBHP (82 µL, 0.6 mmol, 3.0 equiv) was added to the reaction mixture via micro-litter syringe. The reaction mixture was allowed to stir for 36 h at room temperature. After completion (as indicated by TLC), the reaction mixture was quenched with $NaHCO_3$. Then the reaction mixture was poured into water (40 mL) and extracted with ethyl acetate (40 mL). The organic layer was washed with water (10 mL) and brine (10 mL), dried over anhydrous $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography using ethyl acetate/hexane as eluent to afford the desired product.

**Phenyl(2-(pyridin-2-yl)phenyl)methanone, 7a, Scheme 11**. The same general procedure was followed by using 2-phenylpyridine (31.0 mg, 0.2 mmol, 1.0 equiv), palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv), benzaldehyde (32 µL, 0.3 mmol, 1.5 equiv), and aq. *tert*-butyl hydroperoxide (82 µL, 0.6 mmol, 3.0 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a white solid (45.0 mg, 87%), mp 105-107 $^o$C. The spectral data of compound **7a** is in Scheme 9.

**(2-(Pyridin-2-yl)phenyl)(p-tolyl)methanone, 7b, Scheme 11**. The same general procedure was followed by using 2-phenylpyridine (31.0 mg, 0.2 mmol, 1.0 equiv), palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv), 4-methylbenzaldehyde (36 µL, 0.3 mmol, 1.5 equiv), and aq. *tert*-butyl hydroperoxide (82 µL, 0.6 mmol, 3.0 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a white solid (42.5 mg, 78%), 97-99 $^oC$. The spectral data of compound **7b** is in Scheme 9.

**(4-Methoxyphenyl)(2-(pyridin-2-yl)phenyl)methanone, 7e, Scheme 11**. The same general procedure was followed by using 2-phenylpyridine (31.0 mg, 0.2 mmol, 1.0 equiv), palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv), 4-methoxybenzaldehyde (36.5 µL, 0.3 mmol, 1.5 equiv), and aq. *tert*-butyl hydroperoxide (82 µL, 0.6 mmol, 3.0 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a yellowish oil (39.0 mg, 68%). The spectral data of compound **7e** is in Scheme 9.

**1-(4-(2-(Pyridin-2-yl)benzoyl)phenyl)ethanone, 7ac, Scheme 11**. The same general procedure was followed by using 2-phenylpyridine (31.0 mg, 0.2 mmol, 1.0 equiv), palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv), 4-acetylbenzaldehyde (44.5 mg, 0.3 mmol, 1.5 equiv), and aq. *tert*-butyl hydroperoxide (82 µL, 0.6 mmol, 3.0 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a white solid (44.0 mg, 73%), 80-82 $^oC$. $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 8.30 (d, $J$ = 4.8 Hz, 1H), 7.83 (d, $J$ = 8.4 Hz, 2H), 7.80 (d, $J$ = 7.8 Hz, 1H), 7.75 (d, $J$ = 8.4 Hz, 2H), 7.62-7.66 (m, 1H), 7.60 (td, $J$ = 7.8 Hz, 1.2 Hz, 1H), 7.56-7.58 (m, 3H), 7.00-7.02 (m, 1H), 2.57 (s, 3H); $^{13}C$ NMR (150 MHz, CDCl3): $\delta$ 197.6, 197.3, 156.1, 148.8, 141.6, 139.3, 139.2, 139.0, 136.5, 130.5, 129.2, 129.1, 128.8, 128.4, 127.9, 122.2, 122.1, 26.8; IR (neat): $\upsilon_{max}$ 1682, 1433, 1259, 930, 753 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{20}H_{15}NO_2$ $[M]^+$: 301.1103; found: 301.1104.

**Methyl 4-(2-(pyridin-2-yl)benzoyl)benzoate, 7ad, Scheme 11.**[37a] The same general procedure was followed by using 2-phenylpyridine (31.0 mg, 0.2 mmol, 1.0 equiv), palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv), methyl 4-formylbenzoate (49 mg, 0.3 mmol, 1.5 equiv), and aq. *tert*-butyl hydroperoxide (82 µL, 0.6 mmol, 3.0 equiv).

Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a white solid (45.5 mg, 72%). mp 100-102 $^oC$. $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 8.28-8.29 (m, 1H), 7.91 (d, $J$ = 8.4 Hz, 2H), 7.78 (d, $J$ = 7.2 Hz, 1H), 7.71 (d, $J$ = 8.4 Hz, 2H), 7.61-7.64 (m, 1H), 7.54-7.59 (m, 4H), 6.98-7.00 (m, 1H), 3.89 (s, 3H); $^{13}C$ NMR (150 MHz, $CDCl_3$): $\delta$ 197.4, 166.3, 156.1, 148.8, 141.6, 139.4, 139.0, 136.5, 132.8, 130.5, 129.2, 128.9, 128.8, 128.4, 122.2, 122.1, 52.3; IR (neat): $\upsilon_{max}$ 1717, 1664, 1281, 1107, 743 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{20}H_{15}NO_3$ $[M]^+$: 317.1052; found: 317.1053.

**4-(2-(Pyridin-2-yl)benzoyl)benzonitrile, 7ae, Scheme 11.**[32b] The same general procedure was followed by using 2-phenylpyridine (31.0 mg, 0.2 mmol, 1.0 equiv), palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv), 4-formylbenzonitrile (40 mg, 0.3 mmol, 1.5 equiv), and aq. *tert*-butyl hydroperoxide (82 µL, 0.6 mmol, 3.0 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a white solid (26.5 mg, 47%), mp 106-108 $^oC$. $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 8.26 (d, $J$ = 4.2 Hz, 1H), 7.81 (d, $J$ = 7.2 Hz, 1H), 7.74-7.75 (m, 2H), 7.54-7.67 (m, 7H), 7.02-7.04 (m, 1H); $^{13}C$ NMR (150 MHz, $CDCl_3$): $\delta$ 196.4, 155.7, 148.7, 141.6, 139.2, 138.4, 136.7, 131.9, 130.7, 129.2, 129.0, 128.2, 122.3, 122.0, 118.2, 115.0; IR (neat): $\upsilon_{max}$ 2225, 1671, 1285, 929, 744 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{19}H_{12}N_2O$ $[M]^+$: 284.0950; found: 284.0958.

**(3-Nitrophenyl)(2-(pyridin-2-yl)phenyl)methanone, 7af, Scheme 11.**[32b] The same general procedure was followed by using 2-phenylpyridine (31.0 mg, 0.2 mmol, 1.0 equiv), palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv), 3-nitrobenzaldehyde (45 mg, 0.3 mmol, 1.5 equiv), and aq. *tert*-butyl hydroperoxide (82 µL, 0.6 mmol, 3.0 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a colourless oil (34.0 mg, 56%). $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 8.44 (s, 1H), 8.26 (d, $J$ = 4.2 Hz, 1H), 8.22 (d, $J$ = 7.8 Hz, 1H), 8.03 (d, $J$ = 7.8 Hz, 1H), 7.83 (d, $J$ = 7.2 Hz, 1H), 7.58-7.69 (m, 5H), 7.47 (t, $J$ = 7.8 Hz, 1H), 7.00-7.02 (m,1H); $^{13}C$ NMR (150 MHz, $CDCl_3$): $\delta$ 195.5, 155.8, 148.7, 147.9, 139.8, 139.3, 138.2, 136.8, 134.4, 130.8, 129.20, 129.17, 129.0, 128.4, 126.2, 123.6, 122.2, 122.0; IR (neat): $\upsilon_{max}$ 1674, 1531, 1349, 1277, 753 $cm^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{18}H_{12}N_2O_3Na$ $[M + Na]^+$: 327.0746; found: 327.0752.

**Naphthalen-2-yl(2-(pyridin-2-yl)phenyl)methanone, 7ag, Scheme 11.**[17] The same general procedure was followed by using 2-phenylpyridine (31.0 mg, 0.2 mmol, 1.0 equiv), palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv), 2-naphthaldehyde (47 mg, 0.3 mmol, 1.5 equiv), and aq. *tert*-butyl hydroperoxide (82 µL, 0.6 mmol, 3.0 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a colourless oil (37.0 mg, 60%). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.33 (d, $J$ =4.8 Hz, 1H), 8.09 (s, 1H), 7.94 (dd, $J$ = 9.0 Hz, 1.8 Hz, 1H), 7.83 (d, $J$ = 7.2 Hz, 1H), 7.77-7.81 (m, 3H), 7.65-7.67 (m, 1H), 7.62 (dd, $J$ = 7.2 Hz, 1.2 Hz, 1H), 7.51-7.58 (m, 4H), 7.46 (t, $J$ = 7.2 Hz, 1H), 6.93-6.95 (m, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 198.2, 156.7, 149.0, 139.7, 139.6, 136.3, 135.3, 135.2, 132.2, 131.5, 130.2, 129.4, 129.1, 128.8, 128.5, 128.1, 128.0, 127.6, 126.4, 124.9, 122.5, 121.9; IR (neat): $\upsilon_{max}$ 1662, 1588, 1465, 1289, 753 cm$^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{22}H_{15}NO$ $[M]^+$: 309.1154; found: 309.1150.

**(3,4-Dichlorophenyl)(2-(pyridin-2-yl)phenyl)methanone, 7ah, Scheme 11.** The same general procedure was followed by using 2-phenylpyridine (31.0 mg, 0.2 mmol, 1.0 equiv), palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv), 3,4-dichlorobenzaldehyde (52.5 mg, 0.3 mmol, 1.5 equiv), and aq. *tert*-butyl hydroperoxide (82 µL, 0.6 mmol, 3.0 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a white solid (31.5 mg, 48%), mp 135-137 $^o$C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.33 (d, $J$ = 4.2 Hz, 1H), 7.80 (d, $J$ = 7.2 Hz, 1H), 7.78 (d, $J$ = 1.8 Hz, 1H), 7.63-7.66 (m, 2H), 7.59 (d, $J$ = 7.8 Hz, 1H), 7.55 (t, $J$ = 7.2 Hz, 1H), 7.49-7.53 (m, 2H), 7.34 (d, $J$ = 8.4 Hz, 1H), 7.06-7.08 (m, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 195.7, 156.0, 148.8, 139.3, 138.5, 137.8, 136.6, 136.4, 132.5, 130.9, 130.6, 130.1, 129.0, 128.8, 128.4, 128.2, 122.2, 122.1; IR (neat): $\upsilon_{max}$ 1666, 1580, 1434, 1380, 1275, 955, 747 cm$^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{18}H_{11}Cl_2NONa$ $[M + Na]^+$: 350.0115; found: 350.0117.

**(3,4-Dimethoxyphenyl)(2-(pyridin-2-yl)phenyl)methanone, 7ai, Scheme 11.** The same general procedure was followed by using 2-phenylpyridine (31.0 mg, 0.2 mmol, 1.0 equiv), palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv), 3,4-dimethoxybenzaldehyde (50 mg, 0.3 mmol, 1.5 equiv), and aq. *tert*-butyl hydroperoxide (82 µL, 0.6 mmol, 3.0 equiv). Column chromatography ($SiO_2$, eluting with 7:3

hexane/ethyl acetate) afforded the desired product as a white solid (48.0 mg, 75%). mp 108-110 $^{o}$C. $^{1}$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.42-8.43 (m, 1H), 7.77 (d, *J* = 7.8 Hz, 1H), 7.58-7.60 (m, 1H), 7.56 (td, *J* = 7.8 Hz, 1.8 Hz, 1H), 7.49-7.52 (m, 2H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.44 (d, *J* = 1.8 Hz, 1H), 7.16 (dd, *J* = 8.4 Hz, 2.4 Hz, 1H), 7.03-7.05 (m, 1H), 6.66 (d, *J* = 8.4 Hz, 1H), 3.96 (s, 3H), 3.85 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 197.0, 157.0, 152.7, 149.2, 148.6, 139.51, 139.48, 136.2, 130.8, 130.0, 129.0, 128.9, 128.3, 125.2, 122.9, 121.9, 110.9, 109.6, 55.91, 55.89; IR (neat): $\upsilon_{max}$ 1656, 1588, 1511, 1269, 1128, 753 cm$^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{20}H_{17}NO_3Na$ $[M + Na]^+$: 342.1106; found: 342.1112.

**(4-Methyl-2-(pyridin-2-yl)phenyl)(*p*-tolyl)methanone, 7aj, Scheme 11.** The same general procedure was followed by using 2-(*m*-tolyl)pyridine (34.0 mg, 0.2 mmol, 1.0 equiv), palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv), 4-methylbenzaldehyde (36 µL, 0.3 mmol, 1.5 equiv), and aq. *tert*-butyl hydroperoxide (82 µL, 0.6 mmol, 3.0 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a white solid (46.0 mg, 80%), mp 128-130 $^{o}$C. $^{1}$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.42 (d, *J* = 4.2 Hz, 1H), 7.58-7.61 (m, 3H), 7.53 (td, *J* = 7.8 Hz, 1.8 Hz, 1H), 7.43 (t, *J* = 7.2 Hz, 2H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 2H), 7.01-7.03 (m, 1H), 2.50 (s, 3H), 2.31 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 198.0, 157.2, 149.1, 143.0, 140.3, 139.8, 136.8, 136.1, 135.4, 129.8, 129.7, 129.2, 129.0, 128.7, 123.1, 121.8, 21.6, 21.4; IR (neat): $\upsilon_{max}$ 1661, 1605, 1467, 1286, 931, 756 cm$^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{20}H_{17}NONa$ $[M + Na]^+$: 310.1208; found: 310.1217.

**(4-Methoxy-2-(pyridin-2-yl)phenyl)(*p*-tolyl)methanone, 7ak, Scheme 11.** The same general procedure was followed by using 2-(3-methoxyphenyl)pyridine (37.0 mg, 0.2 mmol, 1.0 equiv), palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv), 4-methylbenzaldehyde (36 µL, 0.3 mmol, 1.5 equiv), and aq. *tert*-butyl hydroperoxide (82 µL, 0.6 mmol, 3.0 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a colourless oil (36.5 mg, 60%). $^{1}$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.43-8.44 (m, 1H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.52-7.55 (m, 2H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.27 (d, *J* = 7.8 Hz, 1H), 7.02-7.07 (m, 4H), 3.93 (s, 3H), 2.31 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 197.3, 161.0, 157.2, 149.1, 142.9, 142.1, 136.1, 135.6,

132.0, 131.3, 129.8, 128.7, 123.4, 122.0, 114.6, 113.7, 55.5, 21.5; IR (neat): $\upsilon_{max}$ 2926, 1659, 1603, 1467, 1284, 1223, 1032, 758 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{20}H_{17}NO_2$ $[M]^+$: 303.1259; found: 303.1256.

**(5-Methyl-2-(pyridin-2-yl)phenyl)(*p*-tolyl)methanone, 7al, Scheme 11.**[47] The same general procedure was followed by using 2-(*p*-tolyl)pyridine (34.0 mg, 0.2 mmol, 1.0 equiv), palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv), 4-methylbenzaldehyde (36 µL, 0.3 mmol, 1.5 equiv), and aq. *tert*-butyl hydroperoxide (82 µL, 0.6 mmol, 3.0 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a colourless oil (40.0 mg, 70%). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.37-8.38 (m, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.53-7.55 (m, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.32 (s, 1H), 7.07 (d, *J* = 8.4 Hz, 2H), 6.99-7.01 (m, 1H), 2.45 (s, 3H), 2.32 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 198.2, 156.8, 149.0, 143.0, 139.6, 138.5, 136.7, 136.1, 135.3, 130.7, 129.7, 129.4, 128.72, 128.70, 122.6, 121.6, 21.6, 21.2; IR (neat): $\upsilon_{max}$ 2923, 1663, 1603, 1463, 1290, 757 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{20}H_{17}NO$ $[M]^+$: 287.1310; found: 287.1316.

**(4-(Pyridin-2-yl)-[1,1'-biphenyl]-3-yl)(*p*-tolyl)methanone, 7am, Scheme 11.** The same general procedure was followed by using 2-([1,1'-biphenyl]-4-yl)pyridine (46.5 mg, 0.2 mmol, 1.0 equiv), palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv), 4-methylbenzaldehyde (36 µL, 0.3 mmol, 1.5 equiv), and aq. *tert*-butyl hydroperoxide (82 µL, 0.6 mmol, 3.0 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a white solid (38.5 mg, 55%), mp 145-147 $^oC$. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.42 (d, *J* = 4.2 Hz, 1H), 7.88 (d, *J* = 7.8 Hz, 1H), 7.84 (dd, *J* = 7.8 Hz, 1.8 Hz, 1H), 7.76 (d, *J* = 1.8 Hz, 1H), 7.67-7.69 (m, 4H), 7.59 (td, *J* = 7.8 Hz, 1.8 Hz, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.39 (t, *J* = 7.2 Hz, 1H), 7.11 (d, *J* = 7.8 Hz, 2H), 7.04-7.06 (m, 1H), 2.34 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 197.9, 156.5, 149.1, 143.2, 141.2, 140.2, 139.7, 138.3, 136.3, 135.2, 129.8, 129.3, 128.9, 128.8, 128.5, 127.9, 127.5, 127.1, 122.6, 121.9, 21.6; IR (neat): $\upsilon_{max}$ 1662, 1596, 1462, 1245, 758 $cm^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{25}H_{19}NONa$ $[M + Na]^+$: 372.1364; found: 372.1364.

**1-(3-(4-Methylbenzoyl)-4-(pyridin-2-yl)phenyl)ethanone, 7an, Scheme 11.** The same general procedure was followed by using 1-(4-(pyridin-2-yl)phenyl)ethanone (39.5 mg, 0.2 mmol, 1.0 equiv), palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv), 4-methylbenzaldehyde (36 µL, 0.3 mmol, 1.5 equiv), and aq. *tert*-butyl hydroperoxide (82 µL, 0.6 mmol, 3.0 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a white solid (28.0 mg, 45%), mp 89-91 $^oC$. $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 8.41-8.42 (m, 1H), 8.19 (dd, $J$ = 7.8 Hz, 1.2 Hz, 1H), 8.07 (d, $J$ = 1.8 Hz, 1H), 7.89 (d, $J$ = 8.4 Hz, 1H), 7.59-7.64 (m, 3H), 7.55 (d, $J$ = 7.8 Hz, 1H), 7.08-7.11 (m, 3H), 2.66 (s, 3H), 2.34 (s, 3H); $^{13}C$ NMR (150 MHz, $CDCl_3$): $\delta$ 197.1, 197.0, 155.6, 149.2, 143.6, 143.5, 140.0, 136.6, 136.5, 134.8, 129.6, 129.5, 129.2, 128.9, 122.9, 122.6, 26.8, 21.6; IR (neat): $\upsilon_{max}$ 2925, 1682, 1599, 1300, 1243, 756 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{21}H_{17}NO_2$ $[M]^+$: 315.1259; found: 315.1248.

**Phenyl(2-(quinolin-2-yl)phenyl)methanone, 7ao, Scheme 11.**[49] The same general procedure was followed by using 2-phenylquinoline (41.0 mg, 0.2 mmol, 1.0 equiv), palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv), benzaldehyde (32 µL, 0.3 mmol, 1.5 equiv), and aq. *tert*-butyl hydroperoxide (82 µL, 0.6 mmol, 3.0 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a white solid (28.5 mg, 46%), mp 118-120 $^oC$. $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 8.07 (d, $J$ = 8.4 Hz, 1H), 7.94 (d, $J$ = 7.8 Hz, 1H), 7.76-7.77 (m, 2H), 7.65-7.74 (m, 4H), 7.57-7.61 (m, 3H), 7.43 (d, $J$ = 7.2 Hz, 1H), 7.31-7.33 (m, 1H), 7.23 (t, $J$ = 7.8 Hz, 2H); $^{13}C$ NMR (150 MHz, $CDCl_3$): $\delta$ 198.2, 156.1, 147.3, 140.3, 139.4, 138.2,136.6, 132.1, 130.1, 129.5, 129.2, 129.04, 128.99, 128.82, 128.80, 127.9, 127.2, 126.54, 126.46, 119.9; IR (neat): $\upsilon_{max}$ 1665, 1596, 1282, 931, 768 $cm^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{22}H_{15}NONa$ $[M + Na]^+$: 332.1051; found: 332.1050.

**(2-(Pyridin-2-yl)phenyl)(thiophen-3-yl)methanone, 7ap, Scheme 11.** The same general procedure was followed by using 2-phenylpyridine (31.0 mg, 0.2 mmol, 1.0 equiv), palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv), thiophene-3-carbaldehyde (26 µL, 0.3 mmol, 1.5 equiv), and aq. *tert*-butyl hydroperoxide (82 µL, 0.6 mmol, 3.0 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a colourless oil (30.0 mg, 56%). $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 8.46

(d, *J* = 4.2 Hz, 1H), 7.77 (d, *J* = 7.2 Hz, 1H), 7.58-7.62 (m, 4H), 7.52 (t, *J* = 7.2 Hz, 1H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.42 (d, *J* = 4.8 Hz, 1H), 7.15-7.16 (m, 1H), 7.07-7.09 (m, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$): *δ* 191.8, 157.0, 149.2, 142.8, 140.0, 139.4, 136.3, 133.9, 130.3, 129.2, 128.7, 128.4, 127.6, 125.8, 122.9, 121.9; IR (neat): $\upsilon_{max}$ 1656, 1586, 1428, 1273, 858, 752 cm$^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{16}H_{11}NSONa$ $[M + Na]^+$: 288.0459; found: 288.0460.

**Furan-2-yl(2-(pyridin-2-yl)phenyl)methanone, 7aq, Scheme 11.**[50] The same general procedure was followed by using 2-phenylpyridine (31.0 mg, 0.2 mmol, 1.0 equiv), palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv), furan-2-carbaldehyde (25 µL, 0.3 mmol, 1.5 equiv), and aq. *tert*-butyl hydroperoxide (82 µL, 0.6 mmol, 3.0 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a colourless oil (21.0 mg, 42%). $^1$H NMR (600 MHz, $CDCl_3$): *δ* 8.49 (d, *J* = 4.8 Hz, 1H), 7.78 (d, *J* = 7.8 Hz, 1H), 7.61-7.66 (m, 3H), 7.52-7.54 (m, 2H), 7.43 (s, 1H), 7.10-7.12 (m, 1H), 6.82 (d, *J* = 3.0 Hz, 1H), 6.34-6.35 (m, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$): *δ* 185.4, 157.1, 152.8, 149.2, 146.5, 139.8, 138.3, 136.4, 130.6, 129.1, 129.0, 128.4, 122.7, 121.9, 119.3, 111.9; IR (neat): $\upsilon_{max}$ 1656, 1566, 1465, 1301, 1019, 753 cm$^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{16}H_{11}NO_2Na$ $[M + Na]^+$: 272.0687; found: 272.0634.

**3-Methyl-1-(2-(pyridin-2-yl)phenyl)butan-1-one, 7w, Scheme 11.** The same general procedure was followed by using 2-phenylpyridine (31.0 mg, 0.2 mmol, 1.0 equiv), palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv), 3-methylbutanal (33 µL, 0.3 mmol, 1.5 equiv), and aq. *tert*-butyl hydroperoxide (82 µL, 0.6 mmol, 3.0 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a colourless oil (31.0 mg, 65%). The spectral data of compound **3w** is in decarboxylative acylation part.

**Cyclohexyl(2-(pyridin-2-yl)phenyl)methanone, 7ar, Scheme 11.**[32a] The same general procedure was followed by using 2-phenylpyridine (31.0 mg, 0.2 mmol, 1.0 equiv), palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv), cyclohexanecarbaldehyde (36.5 µL, 0.3 mmol, 1.5 equiv), and aq. *tert*-butyl hydroperoxide (82 µL, 0.6 mmol, 3.0 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the

desired product as a white solid (46.5 mg, 88%), mp 86-88 $^{o}$C. $^{1}$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.64 (d, $J$ = 4.2 Hz, 1H), 7.76 (t, $J$ = 7.2 Hz, 1H), 7.68 (d, $J$ = 7.8 Hz, 1H), 7.60 (d, $J$ = 7.8 Hz, 1H), 7.51 (t, $J$ = 7.8 Hz, 1H), 7.44 (t, $J$ = 7.8 Hz, 1H), 7.41 (d, $J$ = 7.2 Hz, 1H), 7.23-7.25 (m, 1H), 2.18-2.23 (m, 1H), 1.73 (d, $J$ = 13.2 Hz, 2H), 1.66-1.69 (m, 2H), 1.55 (d, $J$ = 13.2 Hz, 1H), 1.35-1.42 (m, 2H), 1.10-1.17 (m, 1H), 0.94-1.02 (m, 2H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 210.8, 157.2, 149.3, 141.3, 138.1, 136.8, 129.8, 128.7, 128.6, 128.1, 122.3, 122.3, 50.8, 29.1, 25.9, 25.8; IR (neat): $\upsilon_{max}$ 2928, 1687, 1586, 1438, 976, 750 cm$^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{18}H_{19}NONa$ $[M + Na]^+$: 288.1364; found: 288.1361.

**3-Methyl-1-(2-(pyridin-2-yl)phenyl)but-2-en-1-one, 7as, Scheme 11.** The same general procedure was followed by using 2-phenylpyridine (31.0 mg, 0.2 mmol, 1.0 equiv), palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv), 3-methylbut-2-enal (29 µL, 0.3 mmol, 1.5 equiv), and aq. *tert*-butyl hydroperoxide (82 µL, 0.6 mmol, 3.0 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a colourless oil (15.0 mg, 76%). $^{1}$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.64 (d, $J$ = 4.8 Hz, 1H), 7.72 (td, $J$ = 7.8 Hz, 1.8 Hz, 1H), 7.62 (d, $J$ = 7.2 Hz, 1H), 7.58 (d, $J$ = 7.8 Hz, 1H), 7.52-7.54 (m, 1H), 7.46-7.48 (m, 2H), 7.22-7.24 (m, 1H), 6.03 (s, 1H), 2.08 (s, 3H), 1.72 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 196.0, 158.1, 154.8, 149.2, 142.1, 139.4, 136.1, 130.1, 129.5, 128.4, 128.1, 125.3, 123.5, 122.0, 27.5, 20.7; IR (neat): $\upsilon_{max}$ 2926, 1666, 1615, 1434, 1236, 1012, 752 cm$^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{16}H_{15}NONa$ $[M + Na]^+$: 260.1051; found: 260.1057.

**Benzo[h]quinolin-10-yl(phenyl)methanone, 7at, Scheme 11.**[32b] The same general procedure was followed by using benzo[*h*]quinoline (36.0 mg, 0.2 mmol, 1.0 equiv), palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv), benzaldehyde (32 µL, 0.3 mmol, 1.5 equiv), and aq. *tert*-butyl hydroperoxide (82 µL, 0.6 mmol, 3.0 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a white solid (51.5 mg, 91%), mp 148-150 $^{o}$C. $^{1}$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.51 (d, $J$ = 4.2 Hz, 1.8 Hz, 1H), 8.04-8.07 (m, 2H), 7.88 (d, $J$ = 8.4 Hz, 1H), 7.77-7,80 (m, 3H), 7.72 (d, $J$ = 9.0 Hz, 1H), 7.65 (dd, $J$ = 7.2 Hz, 1.2 Hz, 1H), 7.40-7.43 (m, 1H), 7.29-7.32 (m, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 198.6, 147.0, 144.6, 139.2, 138.9,

135.3, 133.8, 131.7, 129.2, 129.0, 128.7, 128.1, 127.8, 127.7, 127.0, 126.4, 126.1, 121.6; IR (neat): $\upsilon_{max}$ 1672, 1417, 1272, 841, 708 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{20}H_{13}NO$ $[M]^+$: 283.0997; found: 283.0993.

**Phenyl(2-(pyrimidin-2-yl)phenyl)methanone, 7x, Scheme 11.** The same general procedure was followed by using 2-phenylpyrimidine (31.5 mg, 0.2 mmol, 1.0 equiv), palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv), benzaldehyde (32 µL, 0.3 mmol, 1.5 equiv), and aq. *tert*-butyl hydroperoxide (82 µL, 0.6 mmol, 3.0 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a white solid (34.0 mg, 65%), mp 129-131 $^oC$. The spectral data of compound **7x** is in decarboxylative acylation part.

**Phenyl(2-(pyridin-2-yloxy)phenyl)methanone, 7au, Scheme 11.**[51] The same general procedure was followed except the reaction was run for 72 hours by using 2-phenoxypyridine (34.0 mg, 0.2 mmol, 1.0 equiv), palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv), benzaldehyde (32 µL, 0.3 mmol, 1.5 equiv), and aq. *tert*-butyl hydroperoxide (82 µL, 0.6 mmol, 3.0 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a colourless oil (12.0 mg, 22%). $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 8.00-8.02 (m, 1H), 7.76 (d, $J$ = 8.4 Hz, 2H), 7.56-7.59 (m, 2H), 7.46-7.52 (m, 2H), 7.30-7.34 (m, 3H), 7.27 (d, $J$ = 8.4 Hz, 1H), 6.86-6.88 (m, 1H), 6.60 (d, $J$ = 8.4 Hz, 1H); $^{13}C$ NMR (150 MHz, $CDCl_3$): $\delta$ 195.3, 163.0, 151.6, 147.0, 139.3, 137.5, 132.8, 132.22, 132.15, 130.3, 129.8, 128.0, 124.7, 122.8, 118.5, 111.5, IR (neat): $\upsilon_{max}$ 1666, 1590, 1432, 1250, 766 $cm^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{18}H_{13}NO_2Na$ $[M + Na]^+$: 298.0844; found: 298.0861.

**(2-(1*H*-Pyrazol-1-yl)phenyl)(phenyl)methanone, 7av, Scheme 11.**[51] The same general procedure was followed by using 1-phenyl-1*H*-pyrazole (29.0 mg, 0.2 mmol, 1.0 equiv), palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv), benzaldehyde (32 µL, 0.3 mmol, 1.5 equiv), and aq. *tert*-butyl hydroperoxide (82 µL, 0.6 mmol, 3.0 equiv). Column chromatography ($SiO_2$, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a white solid (16.0 mg, 32%), mp 82-84 $^oC$. $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 7.58-7.66 (m, 6H), 7.50 (td, $J$ = 7.2 Hz, 1.2 Hz, 1H), 7.43-7.46 (m, 1H), 7.41 (d, $J$ = 1.8 Hz, 1H), 7.30 (t, $J$ = 8.4 Hz, 2H), 6.19 (t, $J$ = 1.8 Hz, 1H); $^{13}C$ NMR (150 MHz, $CDCl_3$): $\delta$

195.8, 141.2, 138.6, 136.7, 133.8, 132.9, 131.2, 129.8, 129.6, 129.0, 128.1, 127.5, 123.2, 107.6; IR (neat): $\upsilon_{max}$ 1669, 1590, 1264, 931, 762 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{16}H_{12}N_2O$ $[M]^+$: 248.0950; found: 248.0947.

**Dehydrogenative acylation reaction in gram scale (Synthesis of phenyl(2-(pyridin-2-yl)phenyl)methanone, 7a, Scheme 11).**

To an oven-dried 100 mL sealed tube, a mixture of 2-phenylpyridines (0.93 mL, 6.5 mmol, 1.0 equiv) and palladium(II)acetate (146 mg, 0. 65 mmol, 0.1 equiv) was taken and dry MeCN (50 mL) was added to it. Then benzaldehyde (1.0 mL, 9.8 mmol 1.5 equiv) was added to the reaction mixture. After few seconds flushing with nitrogen, immediately 70% aq. TBHP (2.6 mL, 19.5 mmol, 3.0 equiv) was added to the reaction mixture via syringe. The vessel was sealed with a screw cap. The reaction mixture was allowed to stir for 36 h at room temperature. After completion (as indicated by TLC), the reaction mixture was quenched with $NaHCO_3$. Then the reaction mixture was poured into water (80 mL) and extracted with ethyl acetate (60x2 mL). The organic layer was washed with water (30x2 mL) and brine (30 mL), dried over anhydrous $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The pure phenyl(2-(pyridin-2-yl)phenyl)methanone (**7a**) was obtained as a white solid in 72% (1.21 g) yield after column chromatography of the crude reaction mixture using ethyl acetate/hexane (7:3) as eluent.

**Control experiments, Scheme 12.**

**The standard decarboxylative acylation reaction with radical scavenger (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl (TEMPO), Scheme 12a.**

To an oven-dried 10 mL sealed tube, a mixture of 2-phenylpyridine (31.5 mg, 0.2 mmol, 1.0 equiv), 2-oxo-2-phenylacetic acid (45 mg, 0.3 mmol, 1.5 equiv), potassium persulfate (108 mg, 0.4 mmol, 2.0 equiv), palladium(II)acetate (4.6 mg, 0.02 mmol, 0.1 equiv) and (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl (TEMPO) (31.5 mg, 0.2 mmol, 1.0 equiv) was taken and dry MeCN (3.0 mL) was added to it. After few seconds flushing with nitrogen, the vessel was sealed with a screw cap. The reaction mixture was allowed to stir for 16 h at room temperature. After that the reaction mixture was quenched with $NaHCO_3$. We did

not detect any desired acylation product (**7a**) by TLC. However, we isolated TEMPO-acyl adduct, 2,2,6,6-tetramethylpiperidin-1-yl benzoate (**10a**) in 74% yield as a white solid from the reaction mixture.

This control experiment suggested that the reaction may proceed via radical pathway and the acyl radical intermediate may form from the corresponding 2-oxo-2-phenylacetic acids.

**2,2,6,6-Tetramethylpiperidin-1-yl benzoate 10a, Scheme 12a.**[16a] Column chromatography ($SiO_2$, eluting with 95:5 hexane/ethyl acetate) afforded the desired product as a white solid (39.0 mg, 74%), mp 85-87 $^oC$. $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 8.08-8.10 (m, 2H), 7.59 (t, $J$ = 7.2 Hz, 1H), 7.47 (t, $J$ = 7.8 Hz, 2H), 1.77-1.82 (m, 2H), 1.67-1.74 (m, 1H), 1.59-1.62 (m, 2H), 1.46-1.49 (m, 1H), 1.29 (s, 6H), 1.13 (s, 6H); $^{13}C$ NMR (150 MHz, $CDCl_3$): $\delta$ 166.4, 132.8, 129.7, 129.5, 128.4, 60.4, 39.0, 31.9, 20.8, 17.0; IR (neat): $\upsilon_{max}$ 2932, 1742, 1452, 1248, 1067, 712 $cm^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{16}H_{23}NO_2Na$ $[M + Na]^+$: 284.1626; found: 284.1628.

**The standard decarbonylative acylation reaction with radical scavenger (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl (TEMPO), Scheme 12a.**

To an oven-dried 10 mL sealed tube, a mixture of 2-phenylpyridine (31.5 mg, 0.2 mmol, 1.0 equiv), 2-oxo-2-phenylacetaldehyde (40 mg, 0.3 mmol, 1.5 equiv), potassium persulfate (108 mg, 0.4 mmol, 2.0 equiv), palladium(II)acetate (4.6 mg, 0.02 mmol, 0.1 equiv) and (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl (TEMPO) (31.5 mg, 0.2 mmol, 1.0 equiv) was taken and dry MeCN (3.0 mL) was added to it. After few seconds flushing with nitrogen, the vessel was sealed with a screw cap. The reaction mixture was allowed to stir for 16 h at room temperature. After that the reaction mixture was quenched with $NaHCO_3$. We did not detect any desired acylation product (**7a**) as indicated by TLC. But we isolated TEMPO-acyl adduct, 2,2,6,6-tetramethylpiperidin-1-yl benzoate (**10a**) in 56% as a white solid from the reaction mixture.

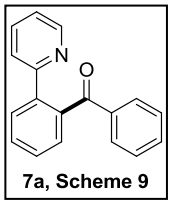
This control experiment suggested that the reaction may proceed via radical pathway and the acyl radical intermediate may form from the corresponding arylglyoxals.

**The standard dehydrogenative acylation reaction with radical scavenger (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl (TEMPO), Scheme 12a.**

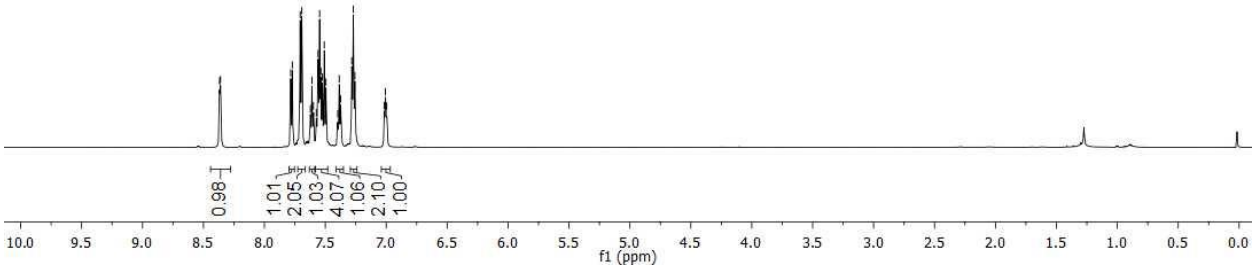
To an oven-dried 7 mL clear vial, a mixture of 2-phenylpyridine (31.5 mg, 0.2 mmol, 1.0 equiv) and palladium(II)acetate (4.6 mg, 0.02 mmol, 0.1 equiv) was taken and dry MeCN (3.0 mL) was added to it. Then benzaldehyde (32.0 µL, 0.3 mmol 1.5 equiv) and (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl (TEMPO) (63.0 mg, 0.4 mmol, 2.0 equiv) was added to the reaction mixture. After flushing with nitrogen, immediately the vessel was sealed with a screw cap. Then aq. TBHP (82 µL, 0.6 mmol, 3.0 equiv) was added to the reaction mixture via micro-litter syringe. The reaction mixture was allowed to stir for 36 h at room temperature. After that the reaction mixture was quenched with $NaHCO_3$. We did not detect any desired acylation product (**7a**) as indicated by TLC. But we isolated TEMPO-acyl adduct, 2,2,6,6-tetramethylpiperidin-1-yl benzoate (**10a**) in 71% as a white solid from the reaction mixture.

When the same experiment was performed with 1.0 equiv of 2,2,6,6-Tetramethylpiperidin-1-yl)oxyl (TEMPO) (31.5 mg, 0.2 mmol), we isolated the desired acylation product (**7a**) in 28% yield and also TEMPO-acyl adduct, 2,2,6,6-tetramethylpiperidin-1-yl benzoate (**10a**) in 90% as a white solid from the reaction mixture. In addition, when the same experiment was performed with 1.5 equiv of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) (47.0 mg, 0.3 mmol), we isolated the desired acylation product (**7a**) in 12% yield and also TEMPO-acyl adduct, 2,2,6,6-tetramethylpiperidin-1-yl benzoate (**10a**) in 75% as a white solid from the reaction mixture. This control experiment suggested that the reaction may proceed via radical pathway and the acyl radical intermediate may form from the corresponding aldehydes.

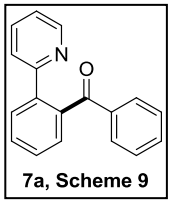
## IV. 8. $^{1}$H and $^{13}$C NMR spectra

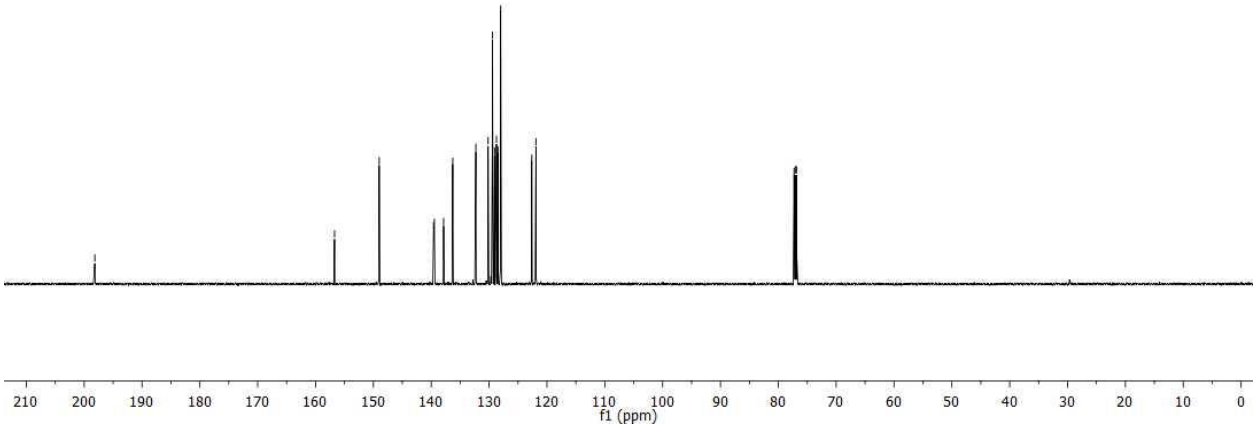

7a, Scheme 9

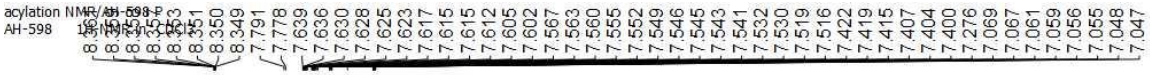


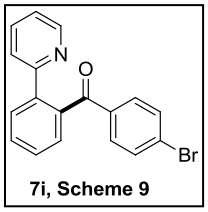




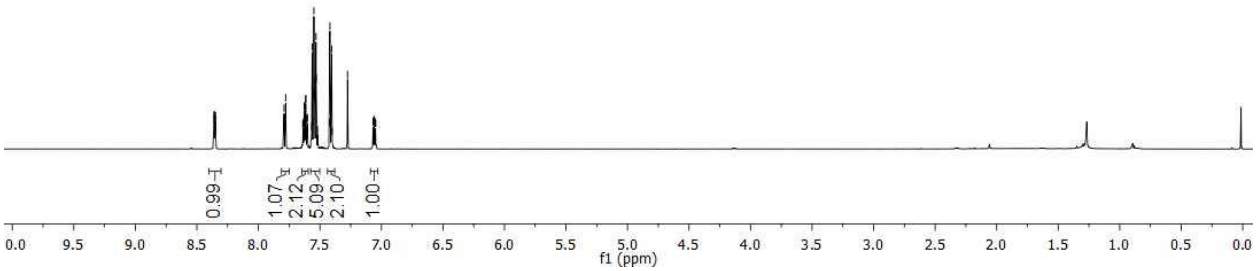

7a, Scheme 9

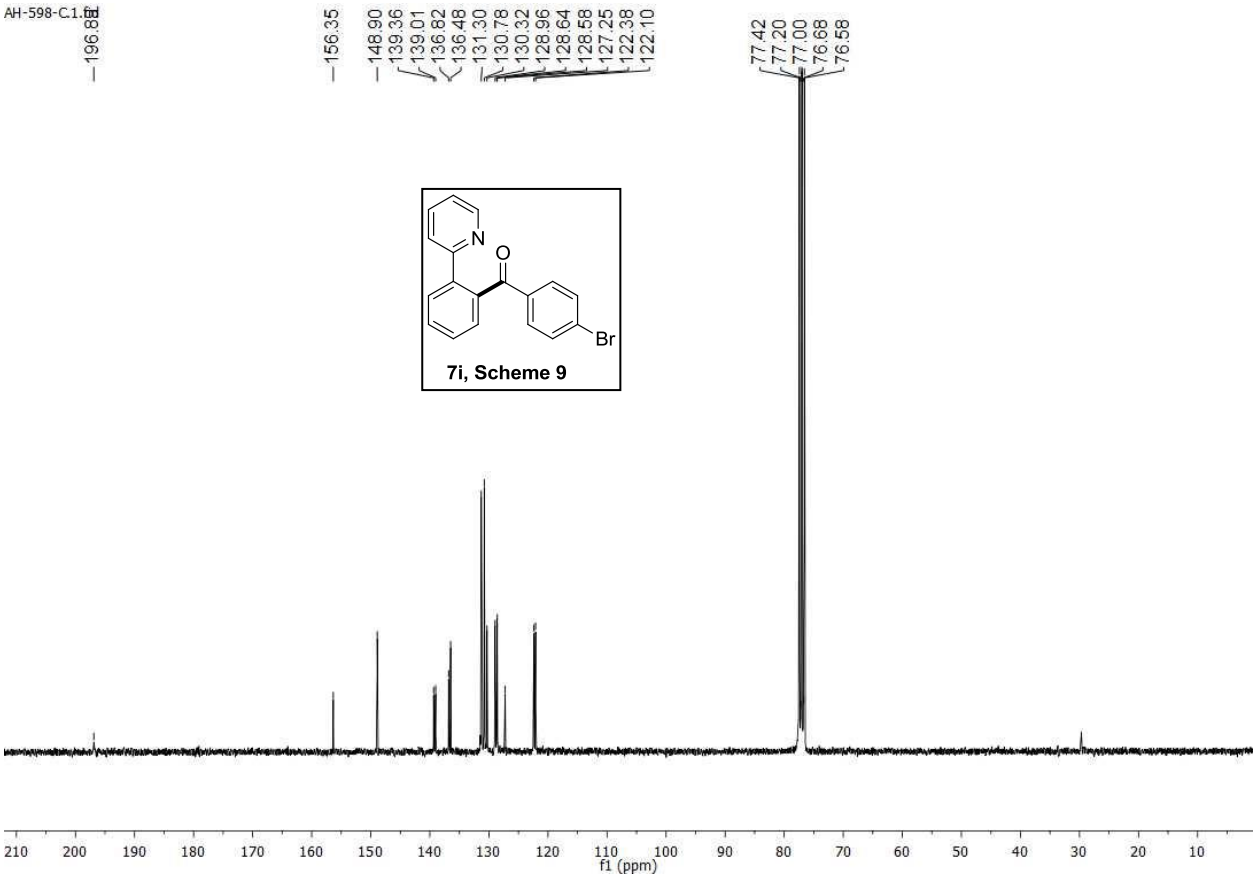





**7i, Scheme 9**




**7i, Scheme 9**


acylation NMR/AH-624 P
AH-624 1H-NMR in CDCl3
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8.397
7.775
7.762
7.608
7.605
7.594
7.581
7.543
7.541
7.531
7.528
7.521
7.508
7.497
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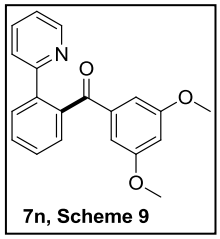
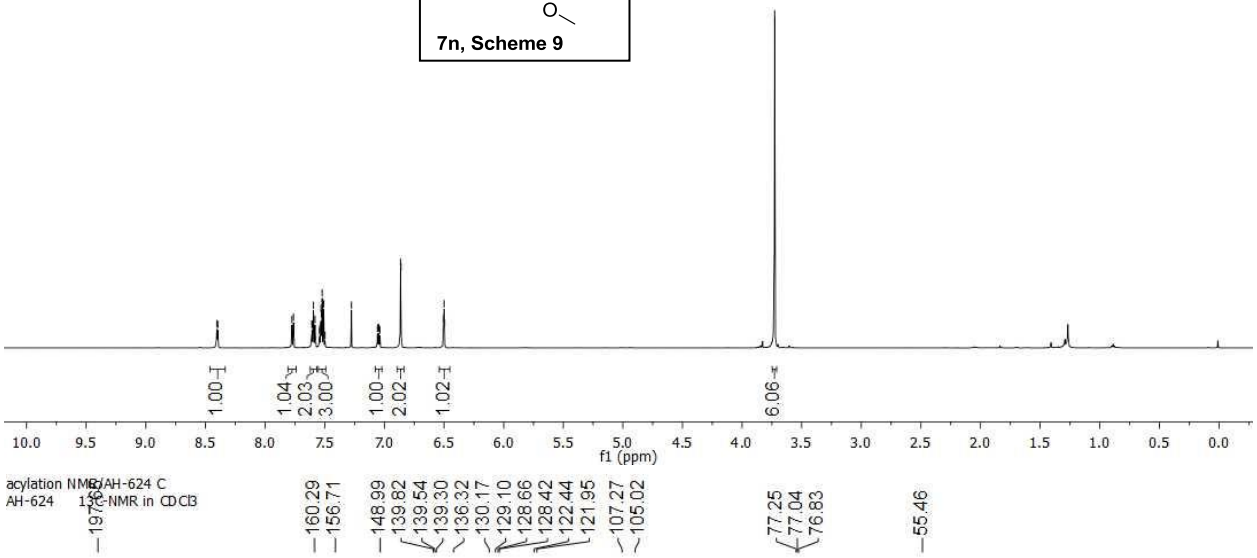
6.499
6.495
3.727


7n, Scheme 9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3.00
1.00
2.02
1.02
6.06
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


acylation NMR/AH-624 C
AH-624 13C-NMR in CDCl3
197.50
160.29
156.71
148.99
139.82
139.54
139.30
136.32
130.17
129.10
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105.02
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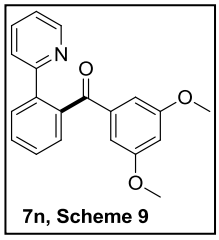
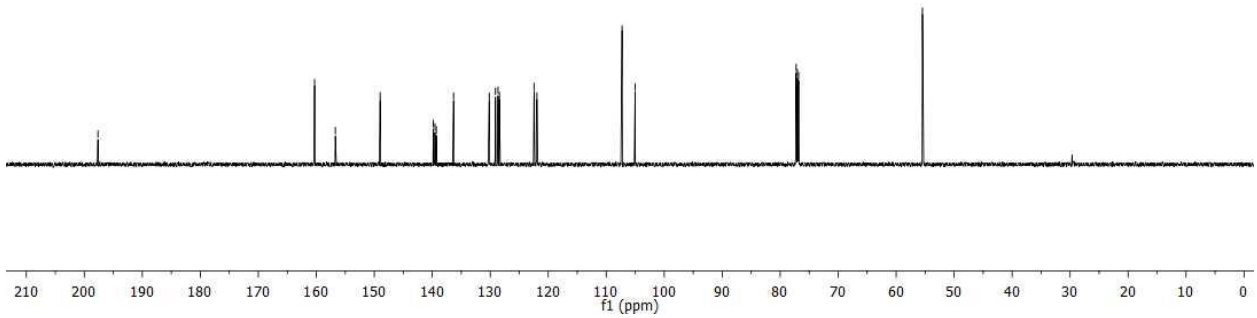
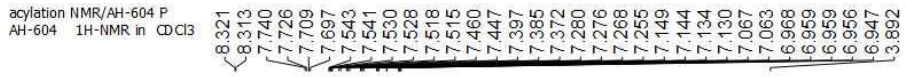
77.04
76.83
55.46


7n, Scheme 9


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


acylation NMR/AH-604 P
AH-604 1H-NMR in CDCl3
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8.313
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7.726
7.709
7.697
7.543
7.541
7.530
7.528
7.518
7.515
7.460
7.447
7.397
7.385
7.372
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7.276
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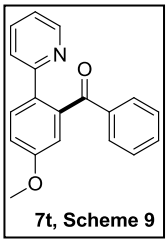
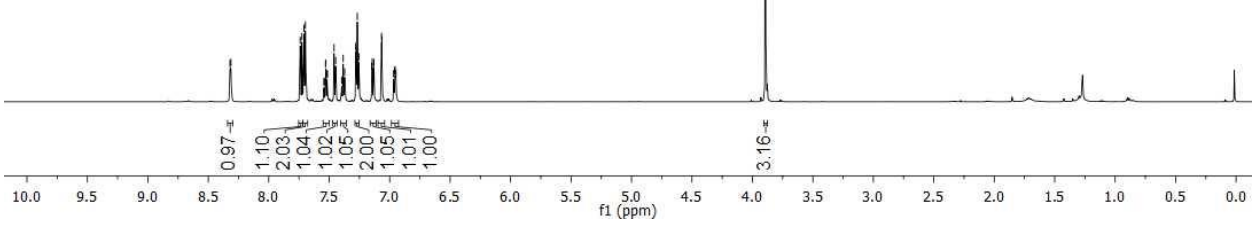
6.947
3.892


N
O
O
7t, Scheme 9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6.5
6.0
5.5
5.0
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2.5
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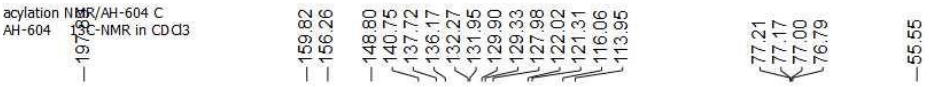
1.0
0.5
0.0
f1 (ppm)


acylation NMR/AH-604 C
AH-604 13C-NMR in CDCl3
197.69
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156.26
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140.75
137.72
136.17
132.27
131.95
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77.21
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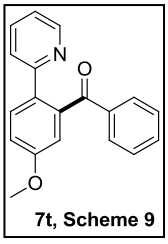
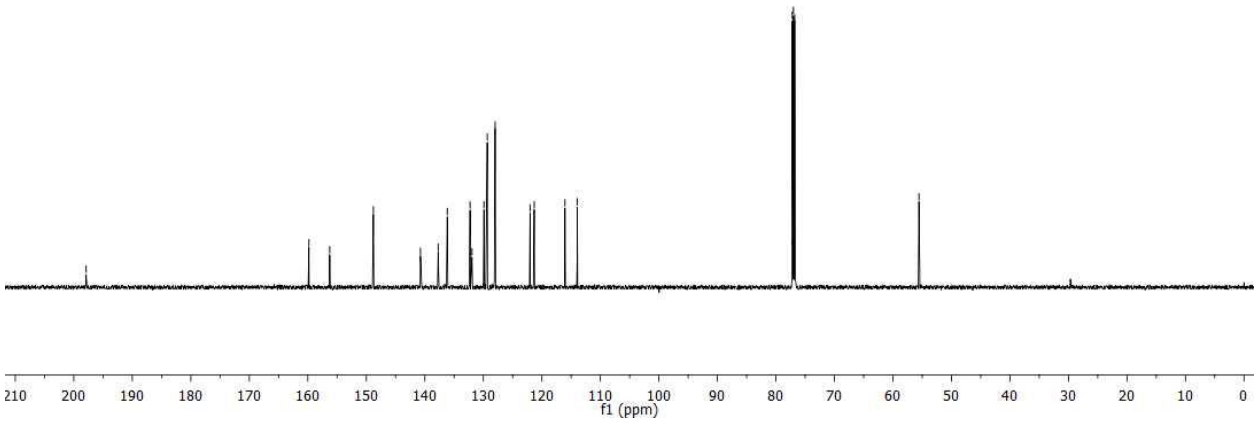
77.00
76.79
55.55


N
O
O
7t, Scheme 9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200
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180
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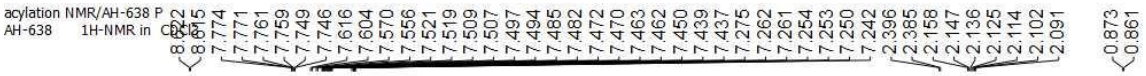
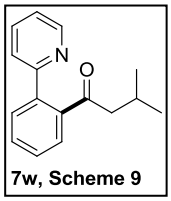
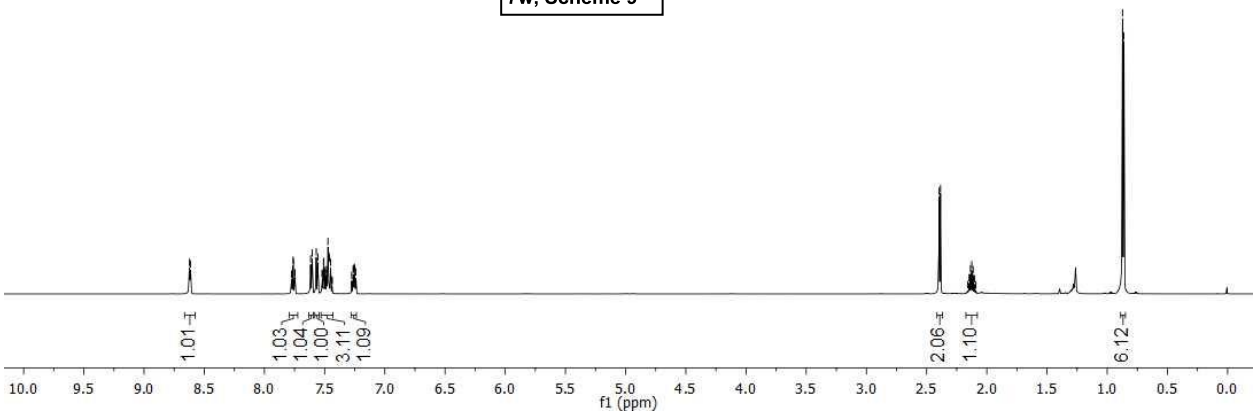
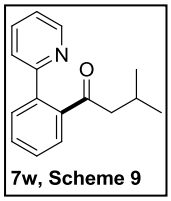
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

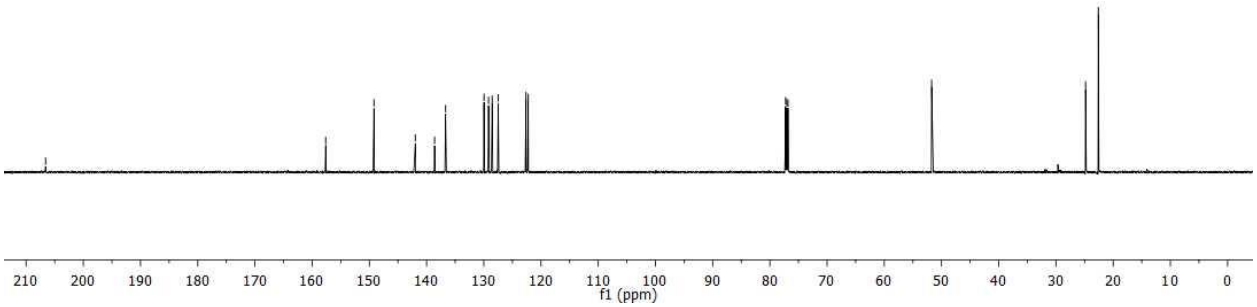

acylation NMR/AH-638 P
AH-638 1H-NMR in CDCl3
8.822
8.815
7.774
7.771
7.761
7.759
7.749
7.746
7.616
7.604
7.570
7.556
7.521
7.519
7.509
7.507
7.497
7.494
7.485
7.482
7.472
7.470
7.463
7.462
7.450
7.439
7.437
7.275
7.262
7.261
7.254
7.253
7.250
7.242
2.396
2.385
2.158
2.147
2.136
2.125
2.114
2.102
2.091
0.873
0.861

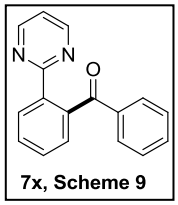

N
O
7w, Scheme 9


1.01
1.03
1.04
1.00
3.11
1.09
2.06
1.10
6.12
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

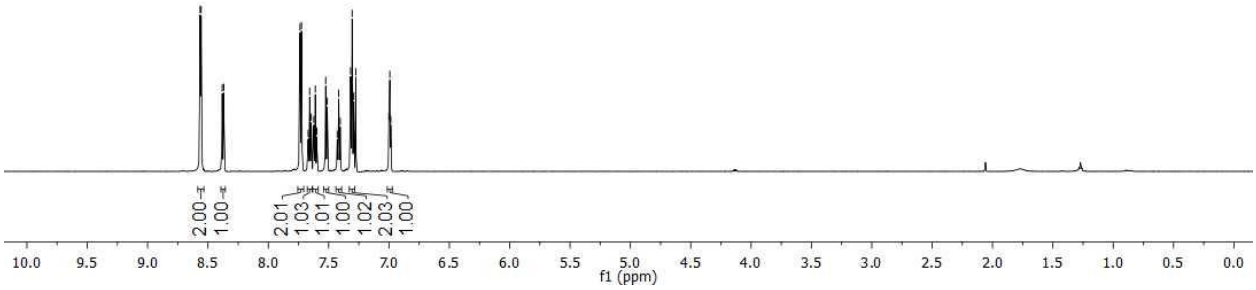

acylation NMR/AH-638 C
AH-638 13C-NMR in CDCl3
206.53
157.63
149.19
141.97
138.60
136.68
129.96
129.17
128.53
127.48
122.62
122.24
77.25
77.04
76.83
51.72
24.82
22.60

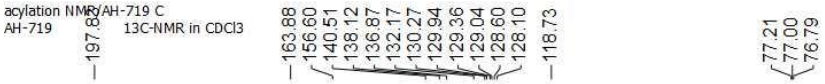

N
O
7w, Scheme 9

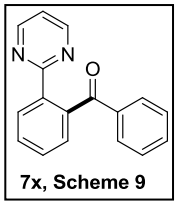

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

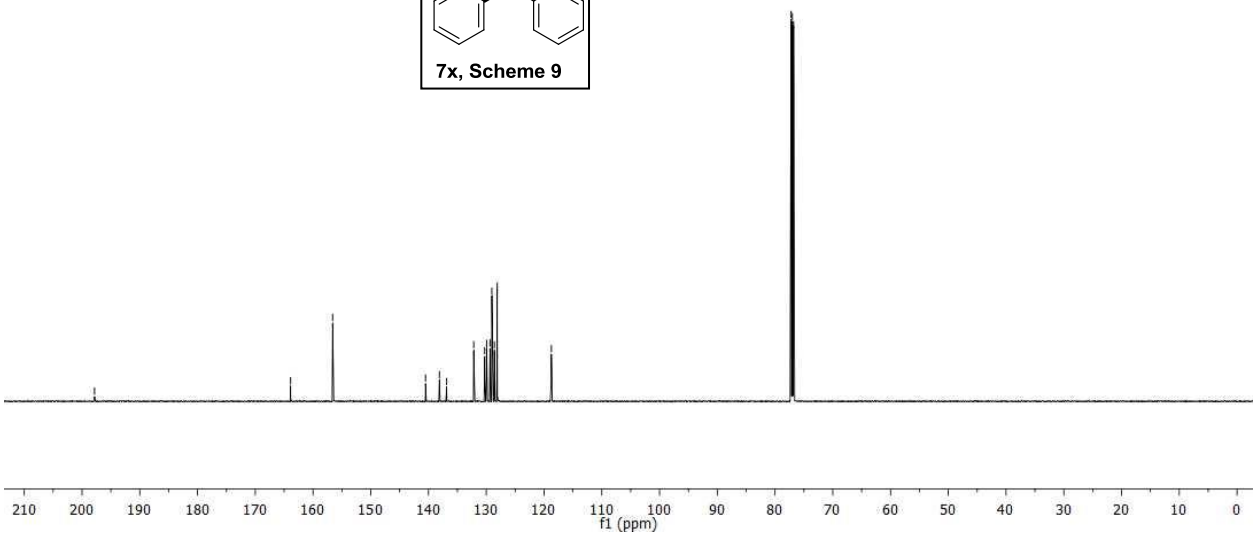

**7x, Scheme 9**




**7x, Scheme 9**



DECARBONYLATIVE NMR DATA/AH-704-P
AH704 1H-NMR in CDCl3

8.359
8.357
7.789
7.787
7.775
7.766
7.698
7.685
7.599
7.597
7.586
7.584
7.573
7.571
7.489
7.476
7.430
7.418
7.405
7.327
7.323
7.313
7.308
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7.275
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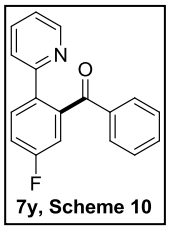
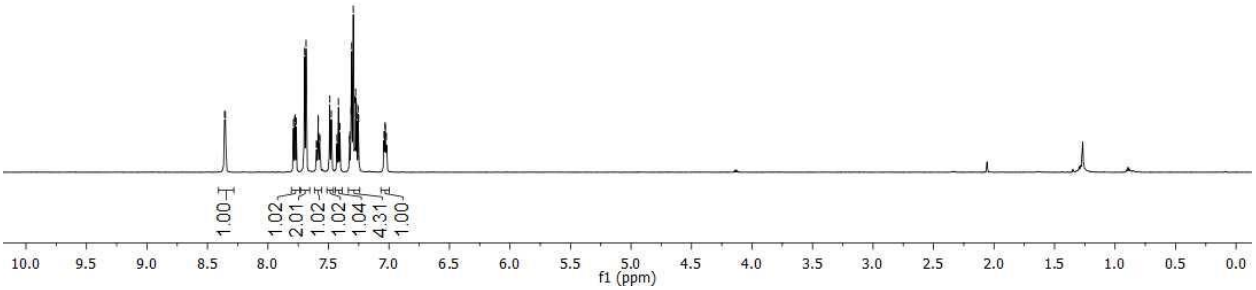
7.265
7.255
7.251
7.041
7.032
7.030
7.021

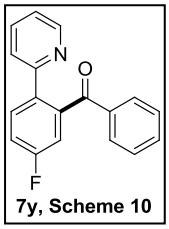



**7y, Scheme 10**

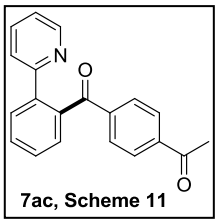



DECARBONYLATIVE NMR DATA/AH-704 C
AH704 13C-NMR in CDCl3

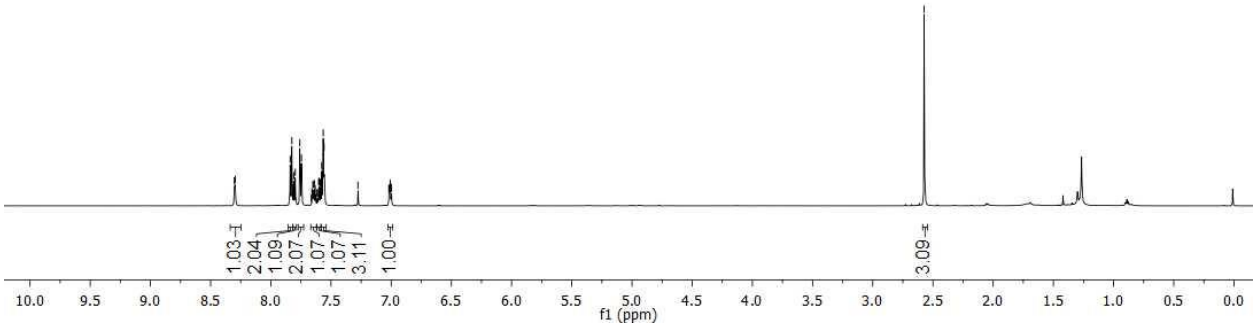
196.41
163.45
161.79
155.63
148.89
141.46
141.43
137.21
136.52
135.54
135.53
132.59
130.61
130.56
129.34
128.14
122.38
121.98
117.15
117.01
116.21
116.06
77.21
77.00
76.79



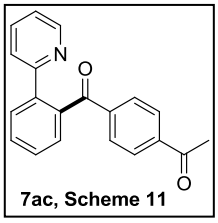

**7y, Scheme 10**

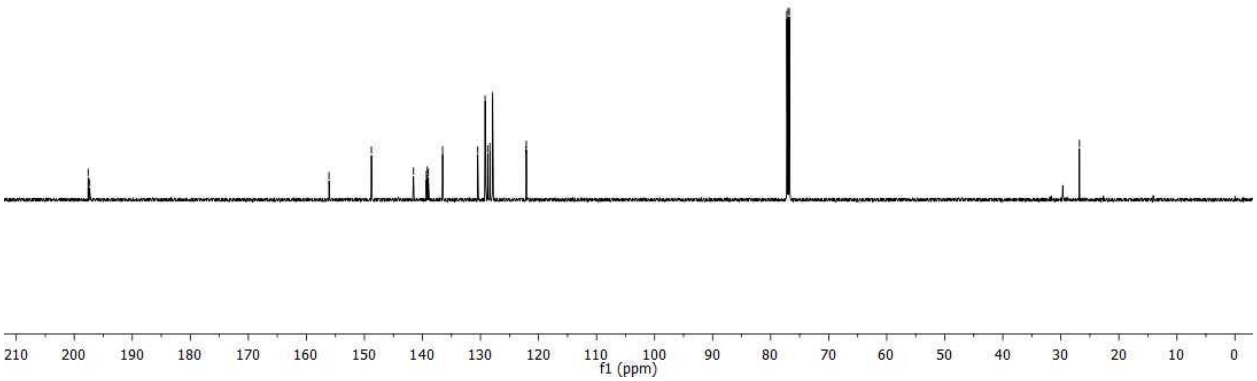

7ac, Scheme 11

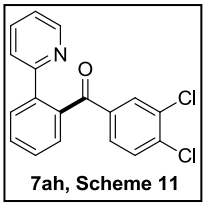




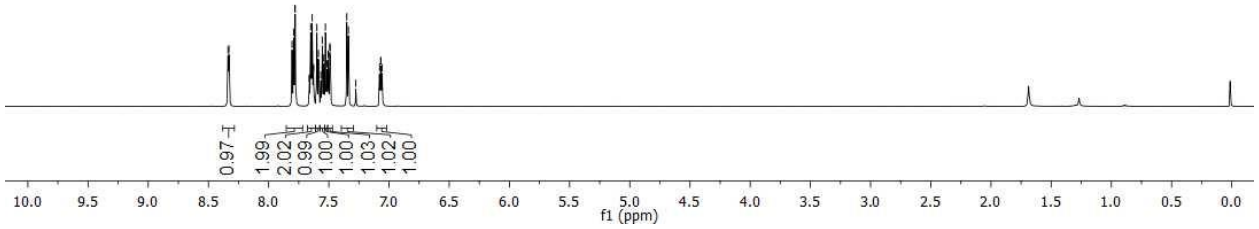


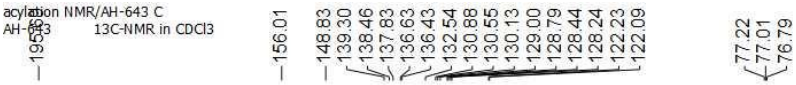

7ac, Scheme 11

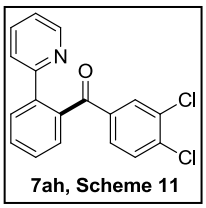


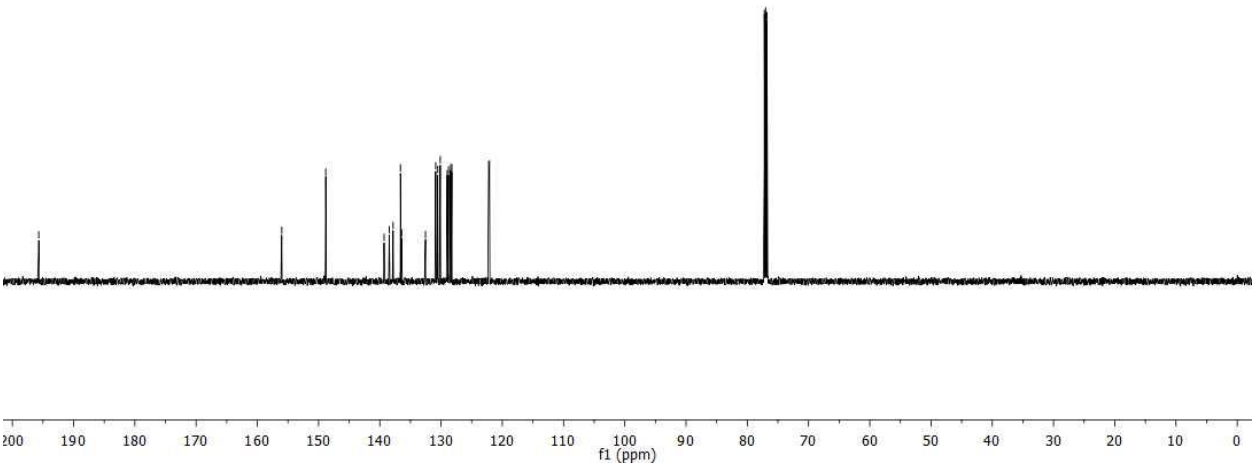

7ah, Scheme 11

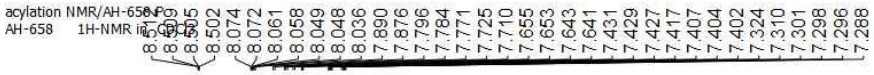


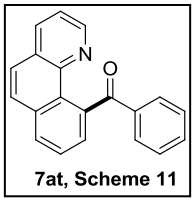



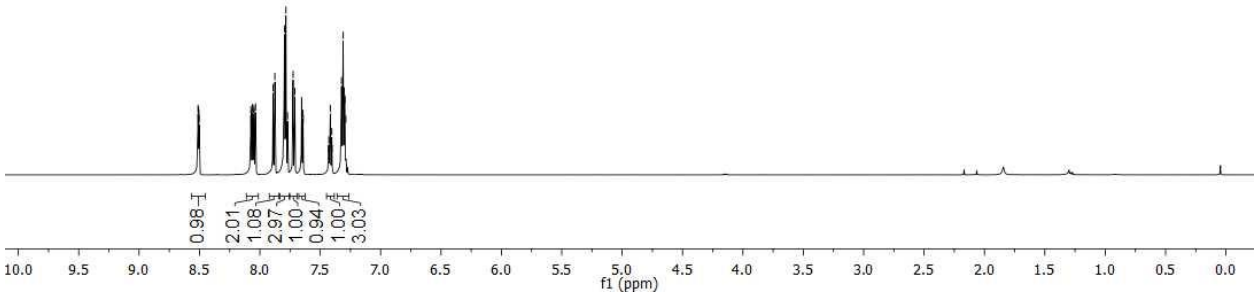

7ah, Scheme 11

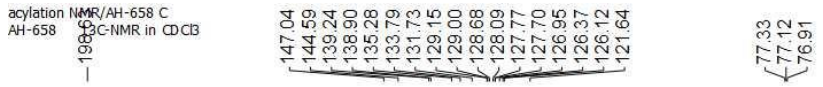


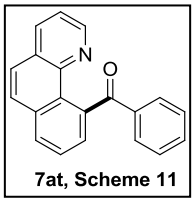


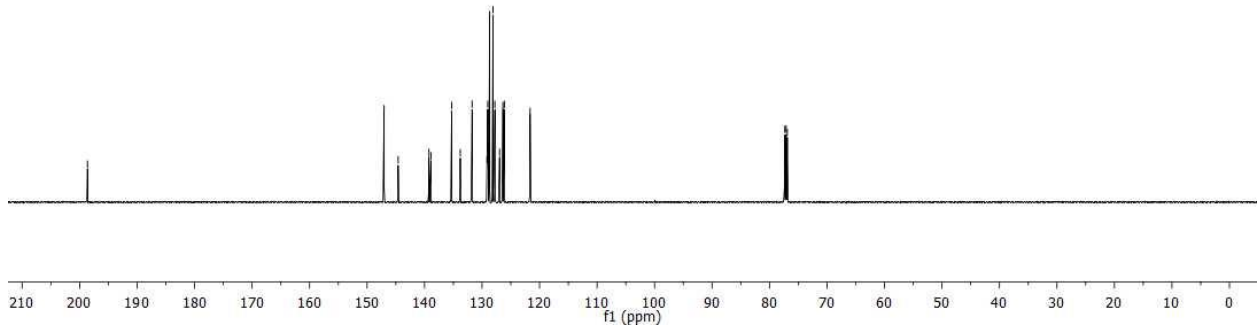

7at, Scheme 11




7at, Scheme 11



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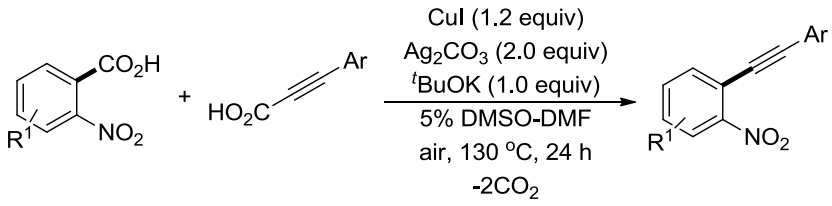
# CHAPTER V

## $Cu^{I}/Ag^{I}$-Promoted Decarboxylative Alkynylation of ortho-Nitro Benzoic Acids



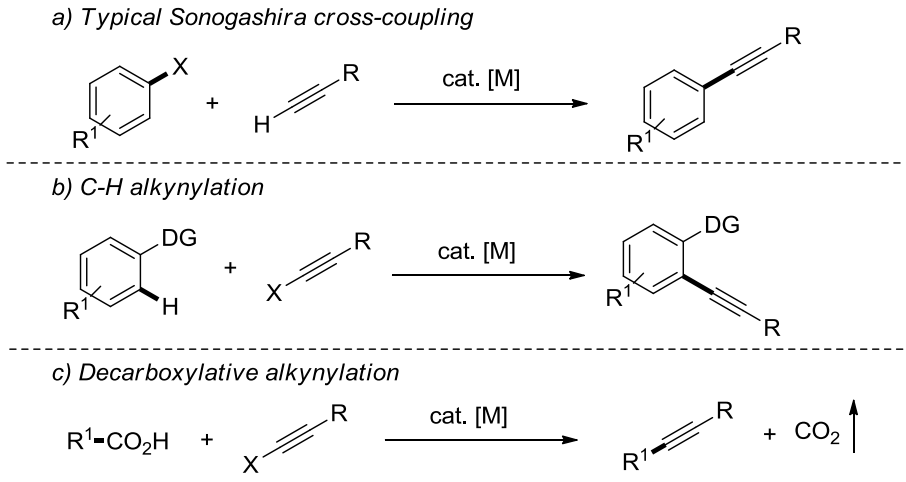

***Abstract:*** We report herein, a novel copper-silver-promoted alkynylation of *ortho*-nitrobenzoic acids with arylacetylenic acids through a double decarboxylation. The present cross-coupling is extremely challanging due to sluggish decarboxylation of arene carboxylates and deleterious oxidative Glaser-Hay type homocoupling of terminal alkynes. Mechanistically, this $sp^2$-*sp* cross-coupling may proceed through a silver-assisted decarboxylation of 2-nitrobenzoic acids followed by transmetalation with copper-acetylide and reductive elimination. The *ortho*-nitroacetylenic product is an important precursor for the synthesis of functionalized indoles.

1. Hossian, A.; Manna, K.; Das, P.; Jana, R. *ChemistrySelect* **2018**, *3*, 4315-4318.

# $Cu^{I}/Ag^{I}$-Promoted Decarboxylative Alkynylation of ortho-Nitro Benzoic Acids

## V. 1. Introduction

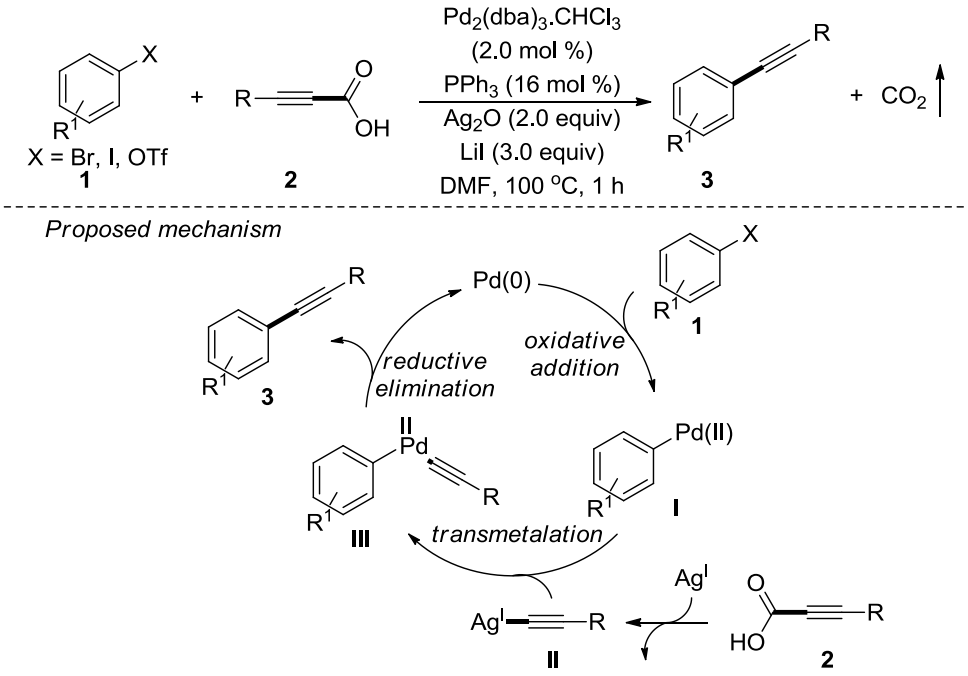
Owing to their unique reactivity as nucleophile as well as electrophile, alkynes are used as one of the most versatile functional groups in organic synthesis and represent an impressive array of utilities in the fuel industry, advanced materials, chemical biology and drug development.[1] However, installation of the alkyne moiety into the organic backbone is heavily dependent on the Sonogashira cross-coupling between vinyl/aryl halides and terminal acetylenes in the presence of palladium/copper(I) bimetallic catalyst.[2] Therefore, development of novel methodology for the synthesis of structurally diverse alkynes is highly desirable. In fact, the direct alkynylation through C-H bonds activation has been investigated in the last decade.[3] But installation of the directing groups to control site-selectivity and their subsequent removal prevents the synthetic fidelity.[4] As an alternative to conventional cross-coupling or C-H functionalization reactions, decarboxylative cross-coupling has emerged as a modern strategy using readily available and inexpensive; air and moisture stable carboxylic acids as coupling partner[5] and have also been successfully accomplished in the alkynylation reactions (Scheme 1).




**Scheme 1.** Alkynylation reactions

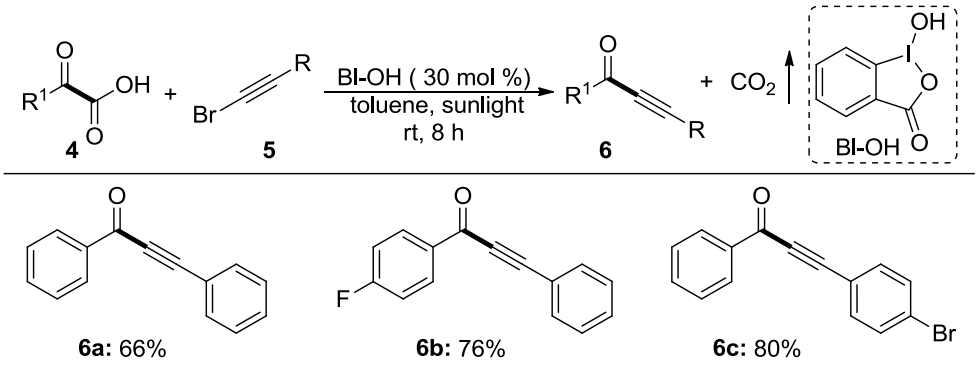
## V. 2. Review

Although, the decarboxylative biaryl and Heck-type cross-coupling have been well-explored but decarboxylative alkynylation remain underdeveloped.[6] In this vein, the Lee group have successfully developed an efficient method for the decarboxylative alkynylation reactions using aryl/vinyl halides and triflates as electrophiles and propiolic acids (Scheme 2).[7] For this transformation, they adopted a palladium/silver bimetallic catalyst system to get synthetically useful yields. Mechanistically, propiolic acids undergo decarboxylation in the presence of silver salt producing silver-acetylides species which may transmetalates with the aryl-Pd(II) intermediate which is formed via oxidative addition of Pd(0) to aryl halides. Finally, the reductive elimination of alkynyl-aryl Pd(II) species provided the desired alkynylated product, regenerating the Pd(0) for next catalytic cycle.

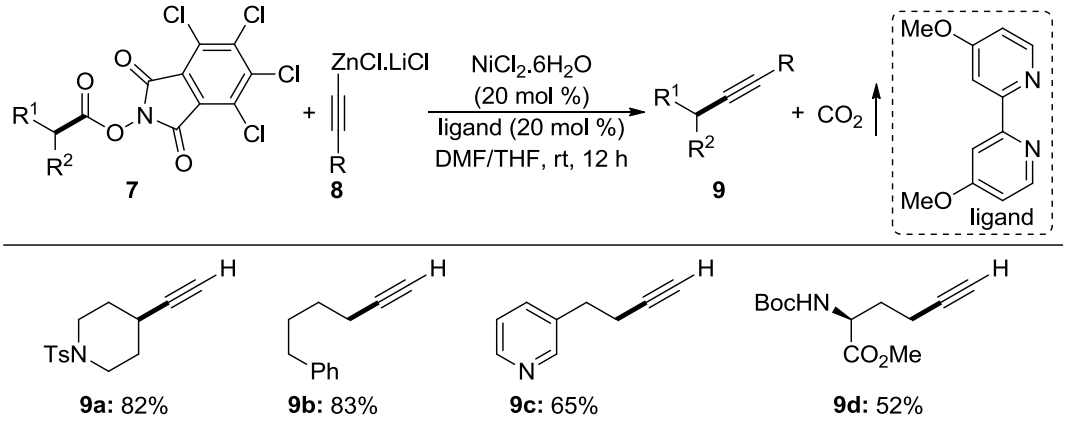



**Scheme 2.** Palladium-catalyzed Decarboxylative alkynylation reaction

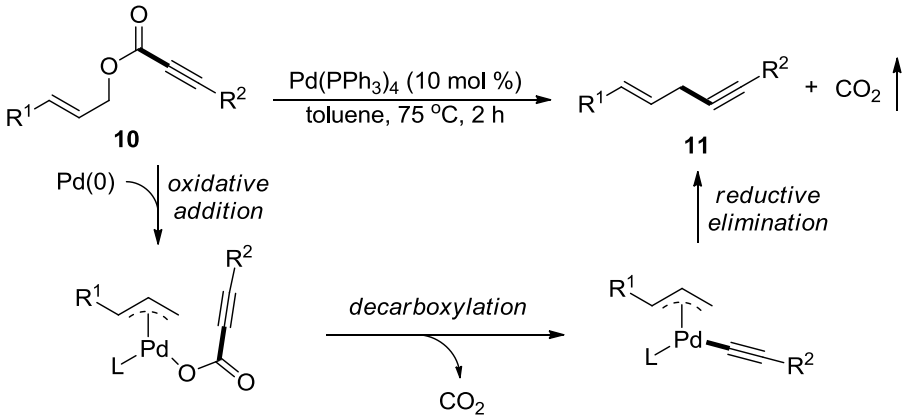
In 2015, Wang and coworkers have reported hypervalent iodine catalyzed sunlight-driven metal free decarboxylative alkynylation of $\alpha$-keto acids with bromoacetylenes to provide variety of ynones with excellent yields (Scheme 3).[8] The sunlight acts as photocatalyst for this transformation and the reaction proceed through acyl radical intermediate formed from the corresponding $\alpha$-oxocarboxylic acids.




**Scheme 3.** Decarboxylative ynone synthesis




**Scheme 4.** Nickel-catalyzed decarboxylative alkynylation reaction




**Scheme 5.** Decarboxylative allylation of propiolic acids

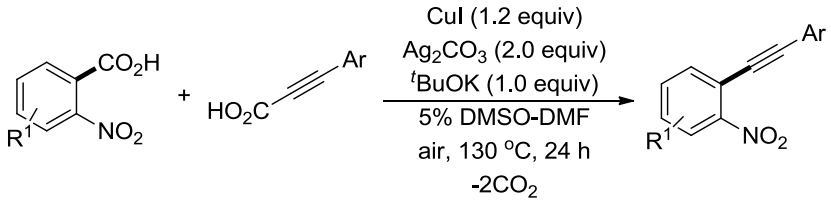
Owing to the prevalence of nickel catalysts towards the decarboxylative cross-coupling reactions,[9] the Baran group has successfully developed a nickel catalyzed

decarboxylative alkynylation reaction using redox-active carboxylic esters and alkynyl zinc reagents (Scheme 4).[10] Interestingly, this method is also applicable to unnatural amino acids and provided a variety of synthetically useful alkyne products.

The Tunge group has also reported palladium catalyzed decarboxylative allylation of propiolic acids derivatives (Scheme 5).[11] The propiolic acids are readily decarboxylate in the presence of palladium catalyst generating palladium-acetylides species which can be coupled with $\pi$-allyl electrophiles to furnish 1,4-enynes via reductive elimination.

## V. 3. Present Work

The three different classes of carboxylic acids have been explored for decarboxylative alkynylation reactions- 1) the propiolic acids undergo decarboxylative metalation to form metal-acetylides for subsequent arylation and heterodiarylation[12] allylation and benzylation;[13] 2) $\alpha$-oxocarboxylic acids serve as an excellent acyl radical equivalent which have also been utilized in the decarboxylative ynone synthesis[14] and recently, 3) alkyl carboxylic acids have showcased tremendous potential in decarboxylative alkynylation reactions under radical conditions.[15] To the best of our knowledge, there is no report of decarboxylative *sp*$^2$-*sp* cross-coupling using arene carboxylic acids. This might be ascribed due to sluggish decarboxylation of arene carboxylates and deleterious oxidative Glaser-Hay type homocoupling of terminal alkynes. For the first time, we report herein a copper(I)/silver(I)-promoted decarboxylative *sp*$^2$-*sp* cross-coupling between 2-nitrobenzoic acid derivatives and alkyne carboxylic acids via *double decarboxylation*. 2-Alkynylated nitroarene product obtained in this protocol is crucial precursor for the synthesis of a plethora of *N*-heterocycles especially functionalized indoles.[16]



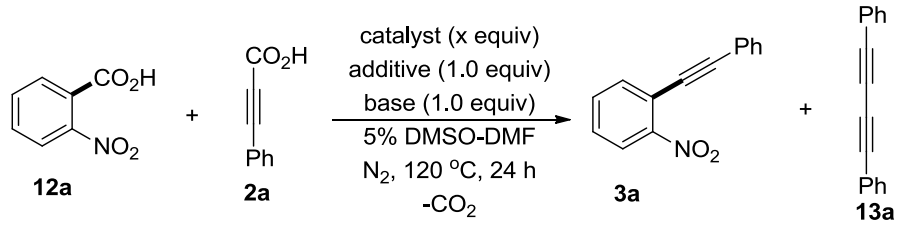

**Scheme 6.** Decarboxylative *sp*$^2$-*sp* alkynylation of *ortho* nitrobenzoic acids

## V. 4. Results and discussion

Initially, 2-nitrobenzoic acid (**12a**, Table 1) and phenyl acetylene were chosen as model substrate for the optimization of decarboxylative alkynylation reaction. However, no desired alkynylation product was obtained except oxidative homocoupling of phenyl acetylene with catalytic palladium(0)/copper(I)iodide. We realized that decarboxylative metalation of nitrobenzoic acid is a slower process compared to copper-assisted homocoupling of phenyl acetylene. To circumvent, we chose phenylpropiolic acid (**2a**, Table 1) to induce parity in decarboxylation steps of two cross-coupling partners.[17] Since palladium did not afford the desired product and silver is known to accelerate decarboxylation process, we decided to use silver(I)/copper(I) bimetallic system which was originally developed by the Goossen's group.[18] Subsequent trials with catalytic copper(I) iodide (20 mol %), in presence of silver(I) carbonate (1.0 equiv) and cesium carbonate (1.0 equiv) afforded decarboxylative protonation of 2-nitrobenzoic acid and 20% of alkyne homocoupling product **13a** (entry 1, Table 1). We hypothesized that sufficient copper-acetylide is essential for the transmetalation with aryl-silver species which is formed through decarboxylation. As expected, increasing the amount of copper(I)iodide to 0.5 and 1.0 equiv the yield of the desired product was increased to 10% and 28% respectively (entry 2 and 3, Table 1). We examined several ligands such as triphenylphosphine, 1,10-phenanthroline, dtbpy etc. with catalytic copper(I) catalyst but did not improved the yield further (entry 4, Table 1). Other copper catalysts such as copper(I) bromide, copper(I) chloride, copper(II) chlorides, copper(II) acetates etc. also afforded interior results (entry 6,7, 20 Table 1). Among the bases screened, potassium-*tert*-butoxide was found to be superior to other bases such as $K_2CO_3$, $NEt_3$, piperidine, pyrrolidine etc. and obtained 40% yield of alkynylation product (**3a**) along with 45% of **13a** (entry 9-12, Table 1). Other solvents such as DMA, DMSO, NMP, $CH_3CN$, etc. and additives provided inferior results (for details see the Supplementary Information). Other several additives were also screened but provided lower yield (entry 13-15, Table 1). Interestingly, the yield of desired alkynylation product (**3a**) was increased to 52% using 1.2 equiv of copper(I) iodide under air (entry 16, Table 1). To accelerate the rate of decarboxylation of 2-nitrobenzoic acid, 2.0 equiv of silver(I) carbonate was necessary

(entry 17, Table 1). Finally heating the reaction mixture at 130 $^{o}$C for 24 h in a combination of 1.2 equiv of copper(I) iodide, 2.0 equiv of silver(I) carbonate and 1.0 equiv of potassium-*tert*-butoxide, the alkynylation product (**3a**) was isolated in 64% yield along with 52% of alkyne homocoupling product (**13a**) (entry 18, Table 1). Interestingly, aerial oxygen was necessary and sufficient for the transformation whereas purging with excess oxygen found to be detrimental (entry 19, Table 1). However, we were unable to suppress alkyne homocoupling product formation even after rigorous screening.

**Table 1.** Optimization of the reaction conditions[a]

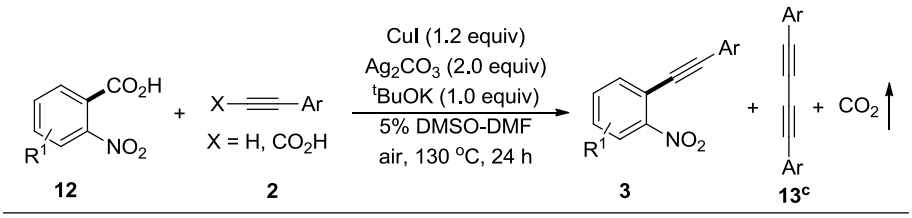



| entry | catalyst | additive | base | yield (%)[b] | |
|---|---|---|---|---|---|
| | | | | **3a** | **13a**[c] |
| 1[d] | CuI (0.2 equiv) | $Ag_2CO_3$ | $Cs_2CO_3$ | 0 | 20 |
| 2 | CuI (0.5 equiv) | $Ag_2CO_3$ | $Cs_2CO_3$ | 10 | 48 |
| 3 | CuI (1.0 equiv) | $Ag_2CO_3$ | $Cs_2CO_3$ | 28 | 42 |
| 4[e] | CuI (1.0 equiv) | $Ag_2CO_3$ | $Cs_2CO_3$ | 0 | 45 |
| 5[f] | CuI (1.0 equiv) | $Ag_2CO_3$ | $Cs_2CO_3$ | nd | 35 |
| 6 | CuCl (1.0 equiv) | $Ag_2CO_3$ | $Cs_2CO_3$ | 20 | 44 |
| 7 | CuBr (1.0 equiv) | $Ag_2CO_3$ | $Cs_2CO_3$ | 18 | 40 |
| 8 | $Pd(tfa)_2$ (0.2 equiv) | $Ag_2CO_3$ | $Cs_2CO_3$ | 0 | 7 |
| 9 | CuI (1.0 equiv) | $Ag_2CO_3$ | $K_2CO_3$ | 20 | 41 |
| 10 | CuI (1.0 equiv) | $Ag_2CO_3$ | pyrrolidine | 30 | 50 |
| 11 | CuI (1.0 equiv) | $Ag_2CO_3$ | $^{t}$BuOK | 40 | 45 |
| 12 | CuI (1.0 equiv) | $Ag_2CO_3$ | $NEt_3$ | 0 | 52 |
| 13 | CuI (1.0 equiv) | $Ag_2O$ | $^{t}$BuOK | 27 | 62 |

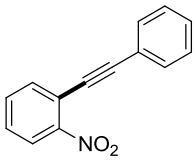
| | | | | | |
|---|---|---|---|---|---|
| 14 | CuI (1.0 equiv) | AgOAc | $^t$BuOK | 5 | 38 |
| 15 | CuI (1.0 equiv) | $K_2S_2O_8$ | $^t$BuOK | 0 | 60 |
| 16[g] | CuI (1.2 equiv) | $Ag_2CO_3$ | $^t$BuOK | 52 | 57 |
| 17[g,h] | CuI (1.2 equiv) | $Ag_2CO_3$ | $^t$BuOK | 60 | 54 |
| **18[g,h,i]** | **CuI (1.2 equiv)** | **$Ag_2CO_3$** | **$^t$BuOK** | **64** | **52** |
| 19[h,i,j] | CuI (1.2 equiv) | $Ag_2CO_3$ | $^t$BuOK | 32 | 55 |
| 20[g,h,i] | $CuCl_2$ (1.2 equiv) | $Ag_2CO_3$ | $^t$BuOK | 30 | 65 |
| 21[g,h,i] | CuI (1.0 equiv) | $Ag_2CO_3$ | - | 0 | 75 |

[a]All reactions were carried out in 0.2 mmol scale using **12a** (1.0 equiv) and **2a** (2.5 equiv). [b]Yields refer to here are isolated yields. [c]% of yield for 1**3a** based on total amount of **2a** was taken. [d]1.5 equiv of **2a** was used. [e]1.0 equiv of $PPh_3$ or 1,10-phenanthroline ligand was used. [f]0.2 equiv of $Ag_2CO_3$ was used. [g]Reaction was run under air. [h]2.0 equiv of $Ag_2CO_3$ was used. [i]The reaction was heated at 130 $^o$C. [j]Reaction was run under $O_2$.

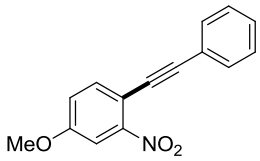
A wide variety of substituents such as alkyl, alkoxyl, chloro on 2-nitrobenzoic acid underwent decarboxylative coupling providing moderate to good yield under the optimized reaction conditions (Scheme 7). To compare, several reactions were also performed with arylacetylenes to furnish the corresponding alkynylation product (Scheme 7). Various substituents on phenylacetylene and/or phenylacetylynic acid such as alkyl (**3g-3i**, **3m**, **3o**, **3q**, **3r**, Scheme 7), aryl (**3j**, Scheme 7), methoxy (**3n**, **3p**, Scheme 7), chloro (**3k**, **3t**, Scheme 7), bromo (**3s**, Scheme 7), fluoro (**3l**, Scheme 7), trifluoromethoxy (**3u**, Scheme 7) were well-tolerated under the reaction conditions. The *ortho* substituted phenylpropiolic acids also took part in the reaction providing high to good yield (**3g**, **3o**, **3q**, Scheme 7). However, other benzoic acids such as *ortho*-methoxybenzoic acid, pentafluorobenzoic acid, *para*-nitrobenzoic acid and heteroaryl carboxylic acids and also alkylated propiolic acids did not furnish any desired product. It was found that the nitro group at *ortho* position of arene carboxylic acids is essential to the desired cross-coupling presumably due the strong inductive effect and coordinating



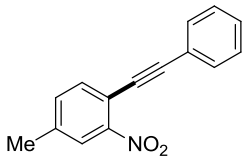

**12** **2** **3** **13**[c]



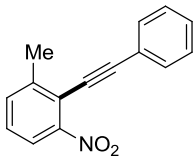
**3a**: X = COOH, 64%
X = H, 60%



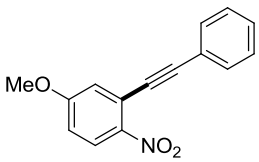

**3b**: X = COOH, 60%
X = H, 58%



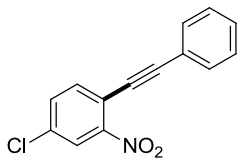

**3c**: X = COOH, 52%



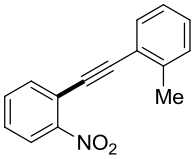

**3d**: X = COOH, 60%



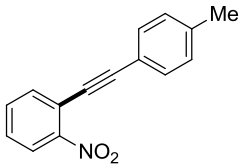

**3e**: X = COOH, 63%



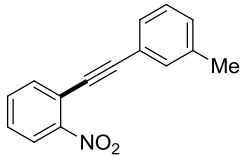

**3f**: X = COOH, 64%



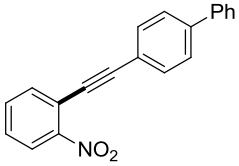

**3g**: X = COOH, 64%



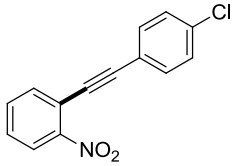

**3h**: X = COOH, 58%
X = H, 62%



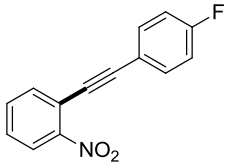

**3i**: X = COOH, 67%



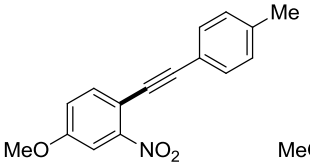

**3j**: X = H, 48%



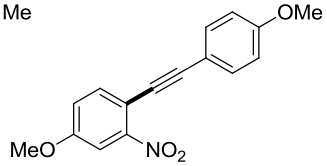

**3k**: X = H, 45%



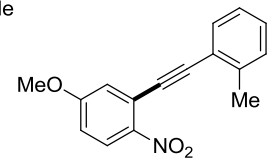

**3l**: X = COOH, 46%



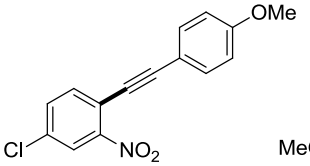

**3m**: X = COOH, 40%



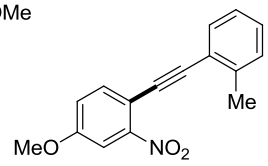

**3n**: X = COOH, 62%



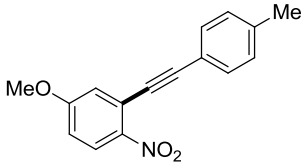

**3o**: X = COOH, 42%



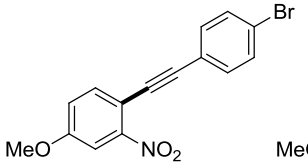

**3p**: X = COOH, 44%



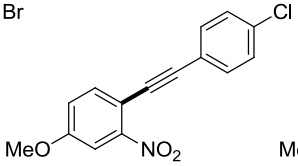

**3q**: X = COOH, 53%



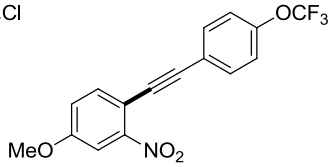

**3r**: X = H, 38%




**3s**: X = H, 60%




**3t**: X = H, 56%




**3u**: X = H, 38%

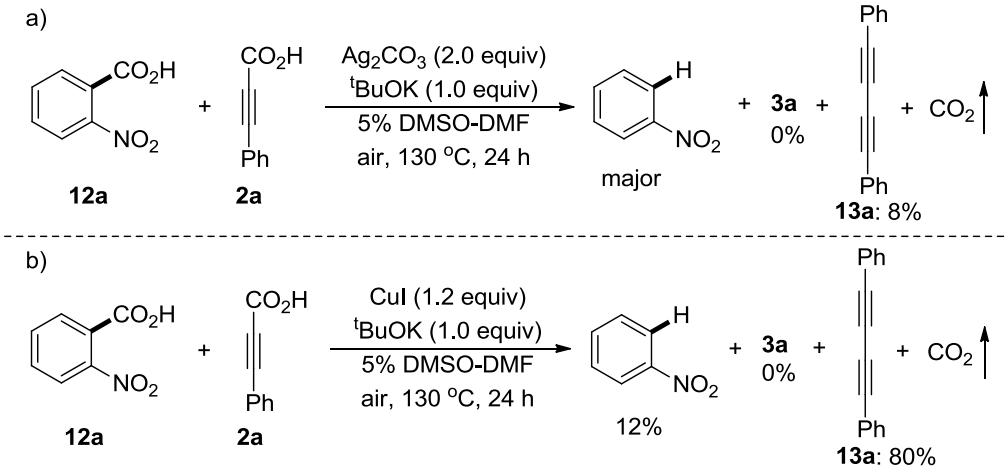
**Scheme 7.** Substrate scope of decarboxylative alkynylation reaction

*Note*: The reactions was carried out in 0.2 mmol scale using **12** (1.0 equiv) and **2** (2.5 equiv). Yields refer to the average of isolated yields of at least two experiments. [c]In every cases 40-50% yield of **13** was separated with respect to total amount of **2** was taken.

ability of the nitro group that may stabilizes the incipient anion which is formed after the decarboxylation. *Ortho* nitrobenzoic acids with another electron-deficient substituent such as 2,4-dinitrobenzoic acid resulted in decarboxylative protonation product only. This indicates that electron withdrawing substituents may facilitate the decarboxylation but they decrease the ability of the aryl anion to serve as a $\sigma$-donor for the copper(II)-acetylide. The same observation was also found in our previous work of decarboxylative allylation of *ortho* nitrobenzoic esters.[19] Selective reduction of nitro group followed by cyclization leads to the formation of 2-phenylindole from **3a** (procedure in experimental section).

## V. 5. Reaction mechanism

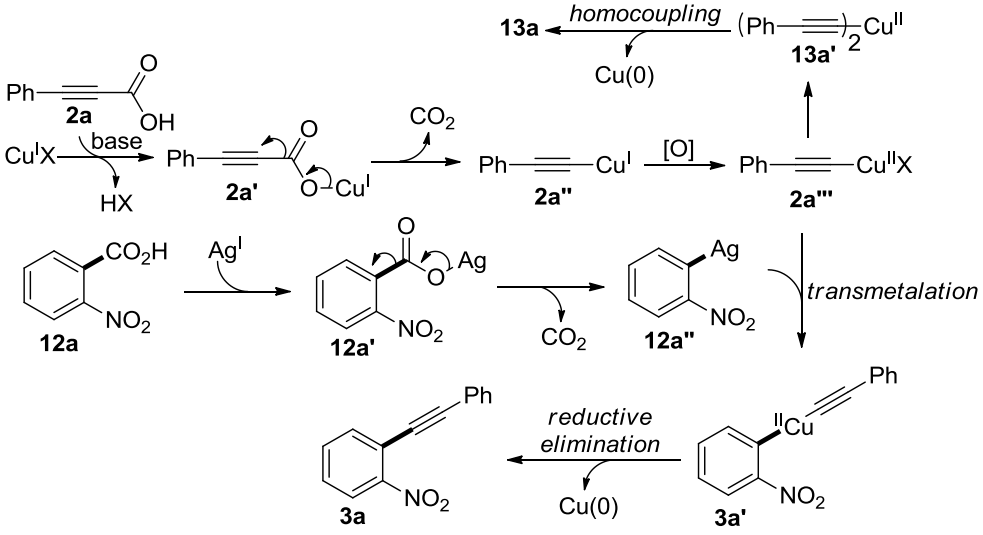
Next, we performed few control experiments to gain insight of the reaction mechanism. The standard reaction without copper salt did not furnish any desired alkynylation product (**3a**) instead nitrobenzene was formed predominantly through decarboxylative protonation and a trace amount of alkyne homocoupling product (**13a**) (Scheme 8a). Furthermore, in the absence of silver salt alkyne homocoupling



**Scheme 8. Control experiments**

Product (**13a**) was favored (80%) along with the formation of nitrobenzene (12%) (Scheme 8b). Therefore, copper is involved in the formation of copper-acetylide via decarboxylation of propiolic acids and silver is participating in the formation of aryl-Ag species via decarboxylation of the nitrobenzoic acids.

Based on these control experiments and previous literature on copper/silver bimetallic system,[18] it is speculated that initially a silver carboxylate forms followed by aryl-silver species, **12a''** (Scheme 9) through the extrusion of $CO_2$. On the other hand, a copper(I)-acetylide, **2a''** (Scheme 9) is formed either via decarboxylative metalation of arylpropiolic carboxylate which is form through base mediated deprotonation of arylpropiolic acid or direct deprotonation of the phenylacetylene by base which is converted to copper(II)-acetylide, **2a'''** (Scheme 9) under the oxidative conditions here aerial oxygen or silver may acts as an oxidant. Subsequently, a transmetalation between aryl-silver and copper(II)-acetylide may leads to the aryl, alkyne-copper intermediate, **3a'** (Scheme 9). There is a possibility of disproportionation to generate copper(III) species for facile reductive elimination at this step and generate a copper(I) species for subsequent runs.[20] However, under the stoichiometric copper catalysis direct reductive elimination from the copper(II) intermediate to furnish the alkynylation product is also plausible. However, the exact mechanism is unclear at this moment



**Scheme 9.** Plausible mechanism

and warrants further studies.

## V. 6. Conclusion

In conclusion, we have developed a novel $Cu^{I}/Ag^{I}$-promoted alkynylation of nitroarenes through a double decarboxylation. This present approach of using two decarboxylations in an oxidative alkynylation is an excellent strategy to address challenging alkynylations. The 2-alkynyl nitroarenes serve as an important precursor for the synthesis of a plethora of *N*-heterocycles especially functionalized indoles.

## V. 7. Experimental section

**General experimental procedure for the preparation of arylalkynecarboxylic acids.[21]**

Propiolic acid (193.0 mg, 2.75 mmol, 1.1 equiv) was diluted with DMSO (1.5 mL). The solution was added to a mixture of $Pd(PPh_3)_4$ (144.5 mg, 0.125 mmol, 0.05 equiv), aryl bromide (2.5 mmol, 1.0 equiv), DBU (0.82 mL, 5.5 mmol, 2.2 equiv), and DMSO (3.5 mL) in a small round-bottom flask. The resulting mixture was stirred at 35 °C for 24 h. After that, the reaction mixture was poured into ethyl acetate (30.0 mL), and extracted with saturated aqueous $NaHCO_3$ solution. The aqueous layer was separated and acidified to pH 2.0 by adding cold HCl (1.0 N), and finally extracted with $CH_2Cl_2$. The organic layer was washed with water (10 mL x 2) and brine (10 mL), dried over anhydrous $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography ($SiO_2$, eluting with 95:5 hexane/ethyl acetate) to afford the desired product as a white solid.

**General experimental procedure for copper(I)/silver(I)-promoted decarboxylative alkynylation of ortho nitrobenzoic acids.**

To an oven-dried 15 mL sealed tube, a mixture of 2-nitrobenzoic acids (0.2 mmol, 1.0 equiv), phenylpropiolic acids and/or phenyl acetylenes (0.5 mmol, 2.5 equiv), copper(I) iodide (46.0 mg, 0.24 mmol, 1.2 equiv), silver (I) carbonate (110 mg, 0.4 mmol, 2.0 equiv) and potassium-*tert*-butoxide (22.5 mg, 0.2 mmol, 1.0 equiv) was taken. Then dry DMF (3.0 mL) and DMSO (0.15 mL) were added to it and the vessel was sealed with a screw cap. The reaction mixture was allowed to stir for 24 h at 130 $^{o}$C. After completion (as detected by TLC), the reaction mixture was poured into water (20 mL) and extracted with ethyl acetate (30 mL). The organic layer was washed with cold water (15 mL x 2) and brine (10 mL), dried over anhydrous $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography using ethyl acetate/hexane as eluent to afford the desired product.

**1-Nitro-2-(phenylethynyl)benzene, 3a, Scheme 7.**[22] The same general procedure was followed by using 2-nitrobenzoic acid (33.5 mg, 0.2 mmol, 1.0 equiv), 3-phenylpropiolic acid (73.0 mg, 0.5 mmol, 2.5 equiv), copper(I) iodide (46.0 mg, 0.24 mmol, 1.2 equiv), silver (I) carbonate (110 mg, 0.4 mmol, 2.0 equiv) and potassium-*tert*-butoxide (22.5 mg, 0.2 mmol, 1.0 equiv). Column chromatography ($SiO_2$, eluting with 95:5 hexane/ethyl acetate) afforded the desired product as a yellow oil, (28.5 mg, 64%). When the same experiment was performed with using ethynylbenzene (55.0 µL, 0.5 mmol, 2.5 equiv) instead of 3-phenylpropiolic acid provided the desired product as a yellow oil (27.0 mg, 60%). $^{1}$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.08 (dd, $J$ = 8.1 Hz, 0.9 Hz, 1H), 7.72 (dd, $J$ = 7.8 Hz, 1.2 Hz, 1H), 7.57-7.63 (m, 3H), 7.46 (td, $J$ = 8.1 Hz, 1.5 Hz, 1H), 7.37-7.39 (m, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 149.6, 134.6, 132.8, 132.0, 129.2, 128.5, 128.4, 124.7, 122.4, 118.8, 97.1, 84.8; IR (neat): $\upsilon_{max}$ 2218, 1606, 1526, 1345, 751 cm$^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{14}H_9NO_2$ $[M]^+$: 223.0633; found: 223.0633.

**4-Methoxy-2-nitro-1-(phenylethynyl)benzene, 3b, Scheme 7.**[23] The same general procedure was followed by using 4-methoxy-2-nitrobenzoic acid (39.5 mg, 0.2 mmol, 1.0 equiv), 3-phenylpropiolic acid (73.0 mg, 0.5 mmol, 2.5 equiv), copper(I) iodide (46.0 mg, 0.24 mmol, 1.2 equiv), silver (I) carbonate (110 mg, 0.4

mmol, 2.0 equiv) and potassium-*tert*-butoxide (22.5 mg, 0.2 mmol, 1.0 equiv). Column chromatography ($SiO_2$, eluting with 95:5 hexane/ethyl acetate) afforded the desired product as a yellow oil, (30.0 mg, 60%). When the same experiment was performed with using ethynylbenzene (55.0 µL, 0.5 mmol, 2.5 equiv) instead of 3-phenylpropiolic acid provided the desired product as yellow oil (29.0 mg, 58%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.56-7.63 (m, 4H), 7.35-7.37 (m, 3H), 7.14 (dd, $J$ = 8.7 Hz, 2.7 Hz, 1H), 3.90 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 159.4, 150.4, 135.5, 131.8, 128.8, 128.4, 122.7, 119.8, 110.8, 109.3, 95.2, 84.7, 56.0.

**4-Methyl-2-nitro-1-(phenylethynyl)benzene, 3c, Scheme 7.**[24] The same general procedure was followed by using 4-methyl-2-nitrobenzoic acid (36.2 mg, 0.2 mmol, 1.0 equiv), 3-phenylpropiolic acid (73.0 mg, 0.5 mmol, 2.5 equiv), copper(I) iodide (46.0 mg, 0.24 mmol, 1.2 equiv), silver (I) carbonate (110 mg, 0.4 mmol, 2.0 equiv) and potassium-*tert*-butoxide (22.5 mg, 0.2 mmol, 1.0 equiv). Column chromatography ($SiO_2$, eluting with 98:2 hexane/ethyl acetate) afforded the desired product as a yellow oil (24.5 mg, 52%). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 7.90 (s, 1H), 7.59-7.62 (m, 3H), 7.41 (d, $J$ = 7.8 Hz, 1H), 7.38-7.39 (m, 3H), 2.47 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 149.4, 139.5, 134.3, 133.7, 131.9, 129.0, 128.4, 125.0, 122.5, 115.8, 96.1, 84.8, 21.2.

**1-Methyl-3-nitro-2-(phenylethynyl)benzene, 3d, Scheme 7.** The same general procedure was followed by using 2-methyl-6-nitrobenzoic acid (36.2 mg, 0.2 mmol, 1.0 equiv), 3-phenylpropiolic acid (73.0 mg, 0.5 mmol, 2.5 equiv), copper(I) iodide (46.0 mg, 0.24 mmol, 1.2 equiv), silver (I) carbonate (110 mg, 0.4 mmol, 2.0 equiv) and potassium-*tert*-butoxide (22.5 mg, 0.2 mmol, 1.0 equiv). Column chromatography ($SiO_2$, eluting with 98:2 hexane/ethyl acetate) afforded the desired product as a yellow oil (28.5 mg, 60%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.85 (d, $J$ = 8.1 Hz, 1H), 7.58-7.61 (m, 2H), 7.51 (d, $J$ = 7.5 Hz, 1H), 7.31-7.39 (m, 4H), 2.62 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 150.6, 143.3, 134.0, 132.0, 129.3, 128.6, 127.9, 122.7, 122.2, 118.2, 101.9, 83.3, 21.5; IR (neat): $\upsilon_{max}$ 2925, 2212, 1528, 1347, 750 $cm^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{15}H_{11}NO_2Na$ $[M + Na]^+$: 260.0687; found: 260.0688.

**4-Methoxy-1-nitro-2-(phenylethynyl)benzene, 3e, Scheme 7.** The same general procedure was followed by using 5-methoxy-2-nitrobenzoic acid (39.5 mg, 0.2 mmol, 1.0 equiv), 3-phenylpropiolic acid (73.0 mg, 0.5 mmol, 2.5 equiv), copper(I) iodide (46.0 mg, 0.24 mmol, 1.2 equiv), silver (I) carbonate (110 mg, 0.4 mmol, 2.0 equiv) and potassium-*tert*-butoxide (22.5 mg, 0.2 mmol, 1.0 equiv). Column chromatography ($SiO_2$, eluting with 95:5 hexane/ethyl acetate) afforded the desired product as a white solid (32.0 mg, 63%), mp 76-78 $^oC$. $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 8.15 (d, $J$ = 9.0 Hz, 1H), 7.62-7.64 (m, 2H), 7.38-7.40 (m, 3H), 7.15 (d, $J$ = 2.4 Hz, 1H), 6.94 (dd, $J$ = 9.0 Hz, 2.4 Hz, 1H), 3.93 (s, 3H); $^{13}C$ NMR (150 MHz, $CDCl_3$): $\delta$ 162.8, 142.6, 132.0, 129.2, 128.4, 127.2, 122.4, 121.0, 118.4, 114.6, 97.0, 85.4, 56.0; IR (neat): $\upsilon_{max}$ 2207, 1583, 1499, 1331, 1232, 756 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{15}H_{11}NO_3$ $[M]^+$: 253.0739; found: 253.0742.

**4-Chloro-2-nitro-1-(phenylethynyl)benzene, 3f, Scheme 7.** The same general procedure was followed by using 4-chloro-2-nitrobenzoic acid (40.5 mg, 0.2 mmol, 1.0 equiv), 3-phenylpropiolic acid (73.0 mg, 0.5 mmol, 2.5 equiv), copper(I) iodide (46.0 mg, 0.24 mmol, 1.2 equiv), silver (I) carbonate (110 mg, 0.4 mmol, 2.0 equiv) and potassium-*tert*-butoxide (22.5 mg, 0.2 mmol, 1.0 equiv). Column chromatography ($SiO_2$, eluting with 99:1 hexane/ethyl acetate) afforded the desired product as a yellowish solid (33.0 mg, 64%), mp 67-69 $^oC$. $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 8.10 (d, $J$ = 1.8 Hz, 1H), 7.67 (d, $J$ = 8.4 Hz, 1H), 7.58-7.61 (m, 3H), 7.38-7.43 (m, 3H); $^{13}C$ NMR (150 MHz, $CDCl_3$): $\delta$ 149.7, 135.4, 134.3, 133.1, 132.0, 129.4, 128.5, 125.0, 122.0, 117.3, 98.2, 83.9; IR (neat): $\upsilon_{max}$ 2924, 2216, 1538, 1344, 1107, 757 $cm^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{14}H_8ClNO_2Na$ $[M + Na]^+$: 280.0141; found: 280.0139.

**1-Methyl-2-((2-nitrophenyl)ethynyl)benzene, 3g, Scheme 7.** The same general procedure was followed by using 2-nitrobenzoic acid (33.5 mg, 0.2 mmol, 1.0 equiv), 3-(*o*-tolyl)propiolic acid (80.0 mg, 0.5 mmol, 2.5 equiv), copper(I) iodide (46.0 mg, 0.24 mmol, 1.2 equiv), silver (I) carbonate (110 mg, 0.4 mmol, 2.0 equiv) and potassium-*tert*-butoxide (22.5 mg, 0.2 mmol, 1.0 equiv). Column chromatography ($SiO_2$, eluting with 99:1 hexane/ethyl acetate) afforded the desired

product as a yellow oil (30.0 mg, 64%). $^{1}$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.11 (d, *J* = 7.8 Hz, 1H), 7.75 (d, *J* = 7.8 Hz, 1H), 7.62 (t, *J* = 7.2 Hz, 1H), 7.58 (d, *J* = 7.2 Hz, 1H), 7.48 (t, *J* = 7.2 Hz, 1H), 7.30 (t, *J* = 7.2 Hz, 1H), 7.27 (d, *J* = 7.2 Hz, 1H), 7.21 (t, *J* = 7.8 Hz, 1H), 2.59 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 149.2, 141.0, 134.7, 132.8, 132.5, 129.6, 129.3, 128.4, 125.6, 124.7, 122.1, 119.0, 96.3, 88.4, 20.7; IR (neat): $\upsilon_{max}$ 2924, 2213, 1525, 1344, 751 $cm^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{15}H_{11}NO_2Na$ $[M + Na]^+$: 260.0687; found: 260.0688.

**1-Nitro-2-(*p*-tolylethynyl)benzene, 3h, Scheme 7.**[24] The same general procedure was followed by using 2-nitrobenzoic acid (33.5 mg, 0.2 mmol, 1.0 equiv), 3-(*p*-tolyl)propiolic acid (80.0 mg, 0.5 mmol, 2.5 equiv), copper(I) iodide (46.0 mg, 0.24 mmol, 1.2 equiv), silver (I) carbonate (110 mg, 0.4 mmol, 2.0 equiv) and potassium-*tert*-butoxide (22.5 mg, 0.2 mmol, 1.0 equiv). Column chromatography ($SiO_2$, eluting with 99:1 hexane/ethyl acetate) afforded the desired product as a white solid, (27.5 mg, 58%). When the same experiment was performed with using 1-ethynyl-4-methylbenzene (63.5 µL, 0.5 mmol, 2.5 equiv) instead of 3-(*p*-tolyl)propiolic acid provided the desired product as a white solid (29.5 mg, 62%), mp 96-98 $^{o}$C. $^{1}$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.09 (d, *J* = 7.8 Hz, 1H), 7.72 (d, *J* = 7.2 Hz, 1H), 7.60 (t, *J* = 7.2 Hz, 1H), 7.51 (d, *J* = 7.8 Hz, 2H), 7.46 (t, *J* = 7.8 Hz, 1H), 7.20 (d, *J* = 7.2 Hz, 2H), 2.40 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 149.5, 139.6, 134.5, 132.8, 131.9, 129.2, 128.3, 124.7, 119.3, 119.0, 97.5, 84.2, 21.6.

**1-Nitro-2-(*m*-tolylethynyl)benzene, 3i, Scheme 7.** The same general procedure was followed by using 2-nitrobenzoic acid (33.5 mg, 0.2 mmol, 1.0 equiv), 3-(*m*-tolyl)propiolic acid (80.0 mg, 0.5 mmol, 2.5 equiv), copper(I) iodide (46.0 mg, 0.24 mmol, 1.2 equiv), silver (I) carbonate (110 mg, 0.4 mmol, 2.0 equiv) and potassium-*tert*-butoxide (22.5 mg, 0.2 mmol, 1.0 equiv). Column chromatography ($SiO_2$, eluting with 99:1 hexane/ethyl acetate) afforded the desired product as a yellowish oil (31.5 mg, 67%). $^{1}$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.10 (dd, *J* = 8.4 Hz, 0.6 Hz, 1H), 7.73 (dd, *J* = 7.8 Hz, 1.2 Hz, 1H), 7.61 (td, *J* = 7.8 Hz, 1.2 Hz, 1H), 7.48 (td, *J* = 8.4 Hz, 1.2 Hz, 1H), 7.44 (s, 1H), 7.42 (d, *J* = 7.8 Hz, 1H), 7.28 (t, *J* = 7.2 Hz, 1H), 7.22 (d, *J* = 7.8 Hz, 1H), 2.38 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$

149.6, 138.2, 134.5, 132.8, 132.6, 130.1, 129.1, 128.4, 128.3, 124.7, 122.1, 118.9, 97.4, 84.4, 21.2; IR (neat): $\upsilon_{max}$ 2924, 2208, 1525, 1344, 784 $cm^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{15}H_{11}NO_2Na$ $[M + Na]^+$: 260.0687; found: 260.0682.

**4-((2-Nitrophenyl)ethynyl)-1,1'-biphenyl, 3j, Scheme 7.** The same general procedure was followed by using 2-nitrobenzoic acid (33.5 mg, 0.2 mmol, 1.0 equiv), 4-ethynyl-1,1'-biphenyl (89.0 mg, 0.5 mmol, 2.5 equiv), copper(I) iodide (46.0 mg, 0.24 mmol, 1.2 equiv), silver (I) carbonate (110 mg, 0.4 mmol, 2.0 equiv) and potassium-*tert*-butoxide (22.5 mg, 0.2 mmol, 1.0 equiv). Column chromatography ($SiO_2$, eluting with 99:1 hexane/ethyl acetate) afforded the desired product as a yellowish solid (28.5 mg, 48%), mp 114-116 $^oC$. $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 8.12 (d, $J$ = 7.8 Hz, 1H), 7.76 (d, $J$ = 7.2 Hz, 1H), 7.69 (d, $J$ = 7.8 Hz, 2H), 7.61-7.64 (m, 5H), 7.47-7.50 (m, 3H), 7.40 (t, $J$ = 7.8 Hz, 1H); $^{13}C$ NMR (150 MHz, $CDCl_3$): $\delta$ 149.5, 141.9, 140.1, 134.6, 132.8, 132.5, 128.9, 128.5, 127.8, 127.1, 127.0, 124.8, 121.2, 118.8, 97.1, 85.5; IR (neat): $\upsilon_{max}$ 2922, 2215, 1521, 1335, 755 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{20}H_{13}NO_2$ $[M]^+$: 299.0946; found: 299.0948.

**1-((4-Chlorophenyl)ethynyl)-2-nitrobenzene, 3k, Scheme 7.** The same general procedure was followed by using 2-nitrobenzoic acid (33.5 mg, 0.2 mmol, 1.0 equiv), 1-chloro-4-ethynylbenzene (68.0 mg, 0.5 mmol, 2.5 equiv), copper(I) iodide (46.0 mg, 0.24 mmol, 1.2 equiv), silver (I) carbonate (110 mg, 0.4 mmol, 2.0 equiv) and potassium-*tert*-butoxide (22.5 mg, 0.2 mmol, 1.0 equiv). Column chromatography ($SiO_2$, eluting with 99:1 hexane/ethyl acetate) afforded the desired product as a yellowish solid (23.0 mg, 45%), mp 94-96 $^oC$. $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 8.11 (d, $J$ = 8.4 Hz, 1H), 7.72 (dd, $J$ = 7.8 Hz, 1.2 Hz, 1H), 7.63 (td, $J$ = 7.2 Hz, 1.2 Hz, 1H), 7.54 (d, $J$ = 8.4 Hz, 2H), 7.50 (td, $J$ = 8.4 Hz, 1.2 Hz, 1H), 7.37 (d, $J$ = 8.4 Hz, 2H); $^{13}C$ NMR (150 MHz, $CDCl_3$): $\delta$ 149.5, 135.4, 134.5, 133.2, 132.9, 128.8, 128.7, 124.8, 120.8, 118.4, 95.8, 85.6; IR (neat): $\upsilon_{max}$ 2212, 1516, 1338, 1082, 823 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{14}H_8ClNO_2$ $[M]^+$: 257.0244; found: 257.0246.

**1-((4-Fluorophenyl)ethynyl)-2-nitrobenzene, 3l, Scheme 7.**[24] The same general procedure was followed by using 2-nitrobenzoic acid (33.5 mg, 0.2 mmol, 1.0 equiv), 3-(4-fluorophenyl)propiolic acid (82.0 mg, 0.5 mmol, 2.5 equiv), copper(I) iodide (46.0 mg, 0.24 mmol, 1.2 equiv), silver (I) carbonate (110 mg, 0.4 mmol, 2.0 equiv) and potassium-*tert*-butoxide (22.5 mg, 0.2 mmol, 1.0 equiv). Column chromatography ($SiO_2$, eluting with 98:2 hexane/ethyl acetate) afforded the desired product as a yellowish solid (22.0 mg, 46%), mp 83-85 $^oC$. $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 8.10 (dd, $J$ = 8.4 Hz, 1.2 Hz, 1H), 7.72 (dd, $J$ = 7.8 Hz, 1.2 Hz, 1H), 7.58-7.64 (m, 3H), 7.49 (t, $J$ = 8.4 Hz, 1.2 Hz, 1H), 7.07-7.11 (m, 2H); $^{13}C$ NMR (150 MHz, $CDCl_3$): $\delta$ 163.0 (d, $J$ = 250.5 Hz), 149.5, 134.4, 134.0 (d, $J$ = 9.0 Hz), 132.8, 128.6, 124.8, 118.6, 118.5 (d, $J$ = 4.5 Hz), 115.8 (d, $J$ = 22.5 Hz), 96.0, 84.5.

**4-Methoxy-2-nitro-1-(*p*-tolylethynyl)benzene, 3m, Scheme 7.**[25] The same general procedure was followed by using 4-methoxy-2-nitrobenzoic acid (39.5 mg, 0.2 mmol, 1.0 equiv), 3-(*p*-tolyl)propiolic acid (80.0 mg, 0.5 mmol, 2.5 equiv), copper(I) iodide (46.0 mg, 0.24 mmol, 1.2 equiv), silver (I) carbonate (110 mg, 0.4 mmol, 2.0 equiv) and potassium-*tert*-butoxide (22.5 mg, 0.2 mmol, 1.0 equiv). Column chromatography ($SiO_2$, eluting with 95:5 hexane/ethyl acetate) afforded the desired product as a yellowish solid (21.0 mg, 40%), mp 64-66 $^oC$. $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 7.62 (d, $J$ = 9.0 Hz, 1H), 7.60 (d, $J$ = 2.4 Hz, 1H), 7.48 (d, $J$ = 7.8 Hz, 2H), 7.19 (d, $J$ = 7.8 Hz, 2H), 7.15 (dd, $J$ = 8.4 Hz, 2.4 Hz, 1H), 3.92 (s, 3H), 2.39 (s, 3H); $^{13}C$ NMR (150 MHz, $CDCl_3$): $\delta$ 159.2, 150.3, 139.1, 135.4, 131.7, 129.2, 119.9, 119.6, 111.2, 109.2, 95.6, 84.2, 56.0, 21.6.

**4-Methoxy-1-((4-methoxyphenyl)ethynyl)-2-nitrobenzene, 3n, Scheme 7.** The same general procedure was followed by using 4-methoxy-2-nitrobenzoic acid (39.5 mg, 0.2 mmol, 1.0 equiv), 3-(4-methoxyphenyl)propiolic acid (88.0 mg, 0.5 mmol, 2.5 equiv), copper(I) iodide (46.0 mg, 0.24 mmol, 1.2 equiv), silver (I) carbonate (110 mg, 0.4 mmol, 2.0 equiv) and potassium-*tert*-butoxide (22.5 mg, 0.2 mmol, 1.0 equiv). Column chromatography ($SiO_2$, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a yellowish solid (35.0 mg,

62%), mp 99-101 $^{o}$C. $^{1}$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.59 (d, $J$ = 6.6 Hz, 1H), 7.58 (s, 1H), 7.49-7.53 (m, 2H), 7.13 (dd, $J$ = 8.7 Hz, 2.7 Hz, 1H), 6.89 (d, $J$ = 9.0 Hz, 2H), 3.90 (s, 3H), 3.84 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 160.1, 159.0, 150.2, 135.3, 133.4, 119.9, 114.8, 114.0, 111.4, 109.2, 95.5, 83.7, 56.0, 55.3; IR (neat): $\upsilon_{max}$ 2211, 1523, 1245, 1028, 831 cm$^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{16}H_{13}NO_4$ $[M]^+$: 283.0845; found: 283.0842.

**4-Methoxy-1-nitro-2-(*o*-tolylethynyl)benzene, 3o, Scheme 7.** The same general procedure was followed by using 5-methoxy-2-nitrobenzoic acid (39.5 mg, 0.2 mmol, 1.0 equiv), 3-(*o*-tolyl)propiolic acid (80.0 mg, 0.5 mmol, 2.5 equiv), copper(I) iodide (46.0 mg, 0.24 mmol, 1.2 equiv), silver (I) carbonate (110 mg, 0.4 mmol, 2.0 equiv) and potassium-*tert*-butoxide (22.5 mg, 0.2 mmol, 1.0 equiv). Column chromatography ($SiO_2$, eluting with 95:5 hexane/ethyl acetate) afforded the desired product as a white solid (22.0 mg, 42%), mp 62-64 $^{o}$C. $^{1}$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.17 (d, $J$ = 9.0 Hz, 1H), 7.59 (d, $J$ = 7.8 Hz, 1H), 7.30 (td, $J$ = 7.8 Hz, 1.2 Hz, 1H), 7.27 (d, $J$ = 6.6 Hz, 1H), 7.21 (t, $J$ = 7.2 Hz, 1H), 7.16 (d, $J$ = 3.0 Hz, 1H), 6.94 (dd, $J$ = 9.0 Hz, 2.4 Hz, 1H), 3.94 (s, 3H), 2.60 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 162.8, 142.3, 141.2, 132.6, 129.6, 129.3, 127.3, 125.6, 122.1, 121.4, 118.6, 114.4, 96.2, 89.0, 56.0, 20.8; IR (neat): $\upsilon_{max}$ 2934, 2208, 1577, 1515, 1337, 1235, 1077, 759 cm$^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{16}H_{13}NO_3$ $[M]^+$: 267.0895; found: 267.0884.

**4-Chloro-1-((4-methoxyphenyl)ethynyl)-2-nitrobenzene, 3p, Scheme 7.** The same general procedure was followed by using 4-chloro-2-nitrobenzoic acid (40.5 mg, 0.2 mmol, 1.0 equiv), 3-(4-methoxyphenyl)propiolic acid (88.0 mg, 0.5 mmol, 2.5 equiv), copper(I) iodide (46.0 mg, 0.24 mmol, 1.2 equiv), silver (I) carbonate (110 mg, 0.4 mmol, 2.0 equiv) and potassium-*tert*-butoxide (22.5 mg, 0.2 mmol, 1.0 equiv). Column chromatography ($SiO_2$, eluting with 95:5 hexane/ethyl acetate) afforded the desired product as a yellowish solid (25.0 mg, 44%), mp 108-110 $^{o}$C. $^{1}$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.07 (d, $J$ = 1.8 Hz, 1H), 7.62 (d, $J$ = 8.4 Hz, 1H), 7.51-7.56 (m, 3H), 6.90 (d, $J$ = 8.7 Hz, 2H), 3.84 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 160.6, 149.5, 135.2, 133.74, 133.69, 133.0, 125.0, 117.7, 114.2, 114.1,

98.8, 83.1, 55.4; IR (neat): $\upsilon_{max}$ 2207, 1516, 1339, 1248, 825 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{15}H_{10}ClNO_3$ $[M]^+$: 287.0349; found: 287.0341.

**4-Methoxy-2-nitro-1-(*o*-tolylethynyl)benzene, 3q, Scheme 7.** The same general procedure was followed by using 4-methoxy-2-nitrobenzoic acid (39.5 mg, 0.2 mmol, 1.0 equiv), 3-(*o*-tolyl)propiolic acid (80.0 mg, 0.5 mmol, 2.5 equiv), copper(I) iodide (46.0 mg, 0.24 mmol, 1.2 equiv), silver (I) carbonate (110 mg, 0.4 mmol, 2.0 equiv) and potassium-*tert*-butoxide (22.5 mg, 0.2 mmol, 1.0 equiv). Column chromatography ($SiO_2$, eluting with 95:5 hexane/ethyl acetate) afforded the desired product as a yellowish oil (28.0 mg, 53%). $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 7.64 (d, $J$ = 9.0 Hz, 1H), 7.61 (d, $J$ = 3.0 Hz, 1H), 7.55 (d, $J$ = 7.2 Hz, 1H), 7.25-7.29 (m, 2H), 7.20 (td, $J$ = 7.2 Hz, 1.8 Hz, 1H), 7.16 (dd, $J$ = 9.0 Hz, 2.4 Hz, 1H), 3.92 (s, 3H), 2.57 (s, 3H); $^{13}C$ NMR (150 MHz, $CDCl_3$): $\delta$ 159.3, 150.0, 140.8, 135.6, 132.3, 129.6, 128.9, 125.6, 122.5, 119.9, 111.2, 109.2, 94.4, 88.4, 56.0, 20.7; IR (neat): $\upsilon_{max}$ 2929, 2211, 1524, 1283, 1030, 758 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{16}H_{13}NO_3$ $[M]^+$: 267.0895; found: 267.0898.

**4-Methoxy-1-nitro-2-(*p*-tolylethynyl)benzene, 3r, Scheme 7.** The same general procedure was followed by using 5-methoxy-2-nitrobenzoic acid (39.5 mg, 0.2 mmol, 1.0 equiv), 1-ethynyl-4-methylbenzene (63.5 µL, 0.5 mmol, 2.5 equiv), copper(I) iodide (46.0 mg, 0.24 mmol, 1.2 equiv), silver (I) carbonate (110 mg, 0.4 mmol, 2.0 equiv) and potassium-*tert*-butoxide (22.5 mg, 0.2 mmol, 1.0 equiv). Column chromatography ($SiO_2$, eluting with 95:5 hexane/ethyl acetate) afforded the desired product as a white solid (20.0 mg, 38%), mp 91-93 $^oC$. $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 8.15 (d, $J$ = 9.0 Hz, 1H), 7.52 (d, $J$ = 8.4 Hz, 2H), 7.20 (d, $J$ = 7.8 Hz, 2H), 7.14 (d, $J$ = 3.0 Hz, 1H), 6.92 (dd, $J$ = 9.0 Hz, 2.4 Hz, 1H), 3.93 (s, 3H), 2.40 (s, 3H); $^{13}C$ NMR (150 MHz, $CDCl_3$): $\delta$ 162.8, 142.6, 139.6, 132.0, 129.2, 127.2, 121.3, 119.3, 118.2, 114.5, 97.4, 85.0, 56.0, 21.6; IR (neat): $\upsilon_{max}$ 2918, 2202, 1570, 1502, 1304, 1075, 752 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{16}H_{13}NO_3$ $[M]^+$: 267.0895; found: 267.0886.

**1-((4-Bromophenyl)ethynyl)-4-methoxy-2-nitrobenzene, 3s, Scheme 7.** The same general procedure was followed by using 4-methoxy-2-nitrobenzoic acid

(39.5 mg, 0.2 mmol, 1.0 equiv), 1-bromo-4-ethynylbenzene (90.0 mg, 0.5 mmol, 2.5 equiv), copper(I) iodide (46.0 mg, 0.24 mmol, 1.2 equiv), silver (I) carbonate (110 mg, 0.4 mmol, 2.0 equiv) and potassium-*tert*-butoxide (22.5 mg, 0.2 mmol, 1.0 equiv). Column chromatography ($SiO_2$, eluting with 97:3 hexane/ethyl acetate) afforded the desired product as a yellowish solid (40.0 mg, 60%), mp 93-95 $^oC$. $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 7.61-7.63 (m, 2H), 7.51 (d, $J$ = 8.4 Hz, 2H), 7.44 (d, $J$ = 8.4 Hz, 2H), 7.16 (dd, $J$ = 9.0 Hz, 3.0 Hz, 1H), 3.92 (s, 3H); $^{13}C$ NMR (150 MHz, $CDCl_3$): $\delta$ 159.6, 150.4, 135.4, 133.2, 131.7, 123.2, 121.7, 119.9, 110.5, 109.4, 94.0, 85.9, 56.0; IR (neat): $\upsilon_{max}$ 2925, 2214, 1528, 1291, 1067, 816 $cm^{-1}$; HRMS (ESI, *m/z*) calcd. for $C_{15}H_{10}BrNO_3Na$ $[M + Na]^+$: 355.9721; found: 355.9719.

**1-((4-Chlorophenyl)ethynyl)-4-methoxy-2-nitrobenzene, 3t, Scheme 7.** The same general procedure was followed by using 4-methoxy-2-nitrobenzoic acid (39.5 mg, 0.2 mmol, 1.0 equiv), 1-chloro-4-ethynylbenzene (68.0 mg, 0.5 mmol, 2.5 equiv), copper(I) iodide (46.0 mg, 0.24 mmol, 1.2 equiv), silver (I) carbonate (110 mg, 0.4 mmol, 2.0 equiv) and potassium-*tert*-butoxide (22.5 mg, 0.2 mmol, 1.0 equiv). Column chromatography ($SiO_2$, eluting with 97:3 hexane/ethyl acetate) afforded the desired product as a yellowish solid (32.0 mg, 56%), mp 76-78 $^oC$. $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 7.62 (d, $J$ = 9.0 Hz, 2H), 7.51 (d, $J$ = 7.8 Hz, 2H), 7.35 (d, $J$ = 8.4 Hz, 2H), 7.16 (dd, $J$ = 8.4 Hz, 1.8 Hz, 1H), 3.92 (s, 3H); $^{13}C$ NMR (150 MHz, $CDCl_3$): $\delta$ 159.6, 150.4, 135.4, 134.9, 133.0, 128.8, 121.2, 119.9, 110.5, 109.4, 94.0, 85.7, 56.0; IR (neat): $\upsilon_{max}$ 2923, 2215, 1530, 1279, 1082, 821 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{15}H_{10}ClNO_3$ $[M]^+$: 287.0349; found: 287.0346.

**4-Methoxy-2-nitro-1-((4-(trifluoromethoxy)phenyl)ethynyl)benzene, 3u, Scheme 7.** The same general procedure was followed by using 4-methoxy-2-nitrobenzoic acid (39.5 mg, 0.2 mmol, 1.0 equiv), 1-ethynyl-4-(trifluoromethoxy)benzene (77.0 µL, 0.5 mmol, 2.5 equiv), copper(I) iodide (46.0 mg, 0.24 mmol, 1.2 equiv), silver (I) carbonate (110 mg, 0.4 mmol, 2.0 equiv) and potassium-*tert*-butoxide (22.5 mg, 0.2 mmol, 1.0 equiv). Column chromatography ($SiO_2$, eluting with 95:5 hexane/ethyl acetate) afforded the desired product as a

yellow oil (25.5 mg, 38%). $^{1}$H NMR (600 MHz, $CDCl_3$): $\delta$ 7.60-7.63 (m, 4H), 7.22 (d, $J$ = 8.4 Hz, 2H), 7.15-7.17 (m, 1H), 3.92 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 159.6, 150.5, 149.2, 135.5, 133.3, 121.5, 120.3 (q, $J$ = 256.5 Hz), 120.9, 119.9, 110.4, 109.4, 93.6, 85.6, 56.0; IR (neat): $\upsilon_{max}$ 2931, 2219, 1525, 1261, 1029, 839 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{16}H_{10}F_3NO_4$ $[M]^+$: 337.0562; found: 337.0568.

**1,4-Diphenylbuta-1,3-diyne, 13a, Scheme 7.[26]** Column chromatography ($SiO_2$, eluting with 99:1 hexane/ethyl acetate) afforded the desired product as a white solid (40.0 mg, 80%). $^{1}$H NMR (600 MHz, $CDCl_3$): $\delta$ 7.55-7.56 (m, 4H), 7.35-7.41 (m, 6H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 132.5, 129.2, 128.4, 121.7, 81.5, 73.9.

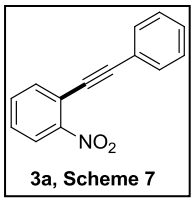
**Preparation of 2-(phenylethynyl)aniline (14a) from 1-nitro-2-(phenylethynyl)benzene (3a) via selective reduction of nitro group. The compound (14a) was synthesized according to the literature procedure.[27]**

To a 10 mL round bottom flask, a mixture of 1-nitro-2-(phenylethynyl)benzene (67.0 mg, 0.3 mmol, 1.0 equiv), indium (III) chloride (27.0 mg, 0.12 mmol, 0.4 equiv) and indium powder (138.0 mg, 1.2 mmol, 4.0 equiv) was taken. Then THF (3.0 mL) and $H_2O$ (0.6 mL) were added to it and the vessel was sealed with a screw cap. The reaction mixture was allowed to stir for 5 h at 50 $^{o}$C. After completion (as detected by TLC), the reaction mixture was poured into water (30 mL) and extracted with ethyl acetate (30 mL). The organic layer was washed with water (15 mL) and brine (10 mL), dried over anhydrous $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography ($SiO_2$, eluting with 95:5 hexane/ethyl acetate) afforded the desired product, 2-(phenylethynyl)aniline (**14a**)[24] as a pale yellowish solid (43.0 mg, 75%). $^{1}$H NMR (600 MHz, $CDCl_3$): $\delta$ 7.55-7.56 (m, 2H), 7.34-7.40 (m, 4H), 7.16 (t, $J$ = 7.8 Hz, 1H), 6.74-6.76 (m, 2H), 4.17 (brs, 2H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 147.6, 132.1, 131.4, 129.7, 128.4, 128.2, 123.3, 118.0, 114.4, 108.0, 94.7, 85.8.

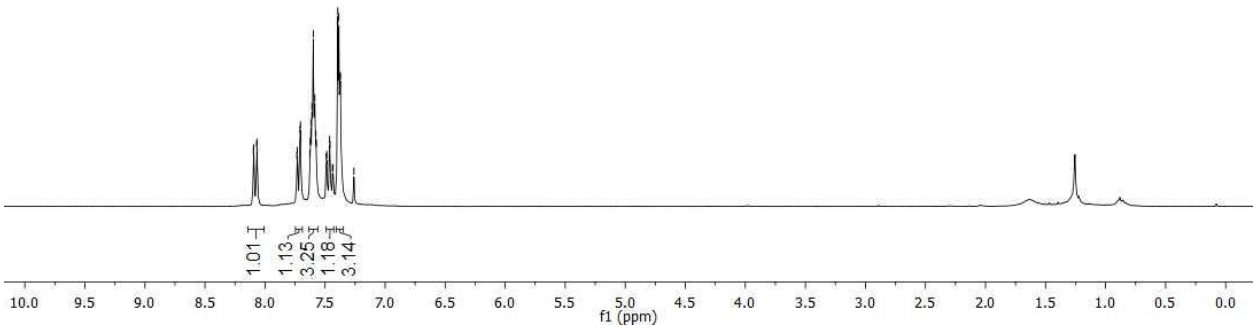
**Direct synthesis of 2-phenylindole (15a) from 1-nitro-2-(phenylethynyl)benzene(3a). The compound (15a) was synthesized according to the literature procedure.[28]**

A solution of 1-nitro-2-(phenylethynyl)benzene (89.0 mg, 0.4 mmol, 1.0 equiv) in pyrrolidine (0.7 mL, 8.0 mmol, 20.0 equiv) was stirred in a 10 mL round bottom flask at 80 °C for 1 h. After removal of pyrrolidine on a rotary evaporator, the residue was dissolved in EtOH (1.0 mL), to which was added Pd/C (4.2 mg, 0.04 mmol, 0.1 equiv). Then the reaction mixture was allowed to stir at 60 $^{o}$C for 10 h under a hydrogen atmosphere. After completion (as detected by TLC), the reaction mixture was filtered through a pad of celite, and concentrated. The crude reaction mixture was purified by column chromatography ($SiO_2$, eluting with 95:5 hexane/ethyl acetate) afforded the desired product, 2-phenylindole (**15a**)[24] as a white solid (46.0 mg, 60%). $^{1}$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.35 (brs, 1H), 7.69 (d, $J$ = 7.8 Hz, 2H), 7.67 (d, $J$ = 7.8 Hz, 1H), 7.47 (t, $J$ = 7.2 Hz, 2H), 7.43 (d, $J$ = 7.8 Hz, 1H), 7.36 (t, $J$ = 7.8 Hz, 1H), 7.23 (t, $J$ = 7.8 Hz, 1H), 7.16 (t, $J$ = 7.8 Hz, 1H), 6.86 (s, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 137.8, 136.8, 132.3, 129.2, 129.0, 127.7, 125.1, 122.3, 120.6, 120.3, 110.9, 100.0.

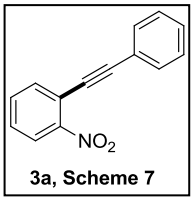
## V. 8. $^{1}$H and $^{13}$C NMR spectra

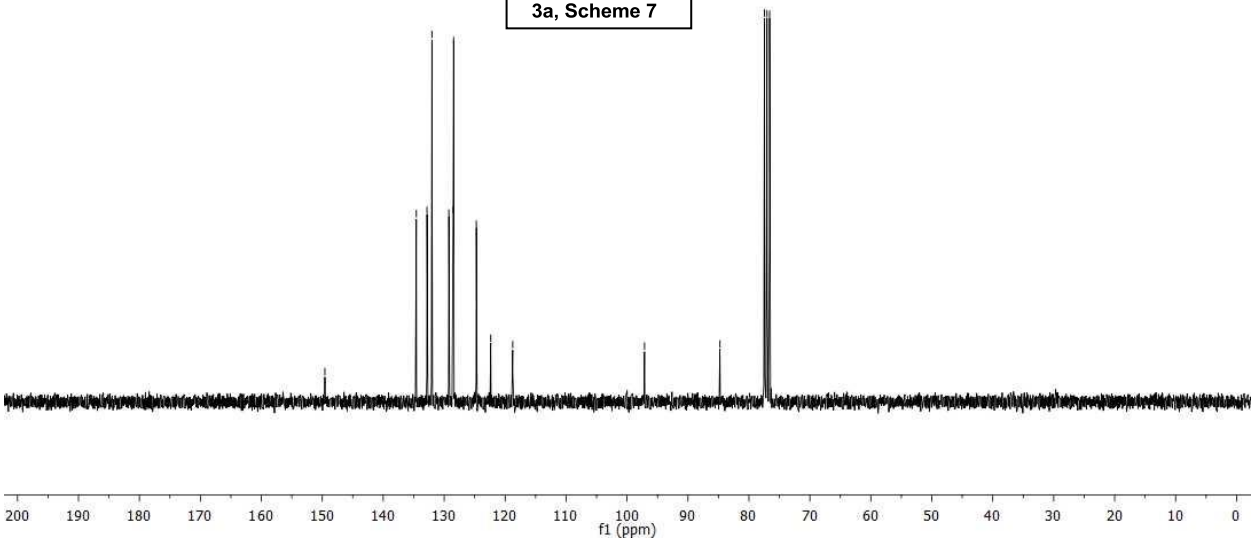

**3a, Scheme 7**

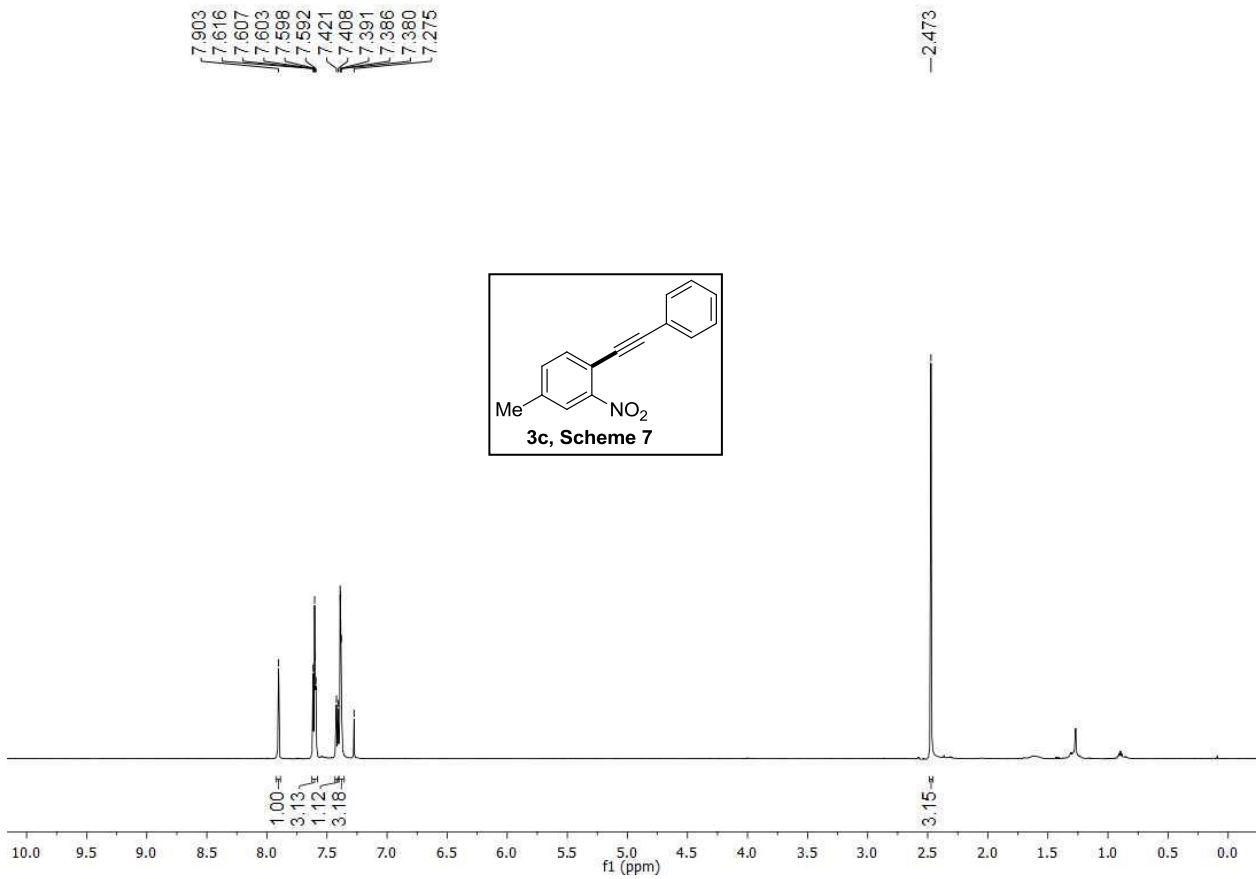


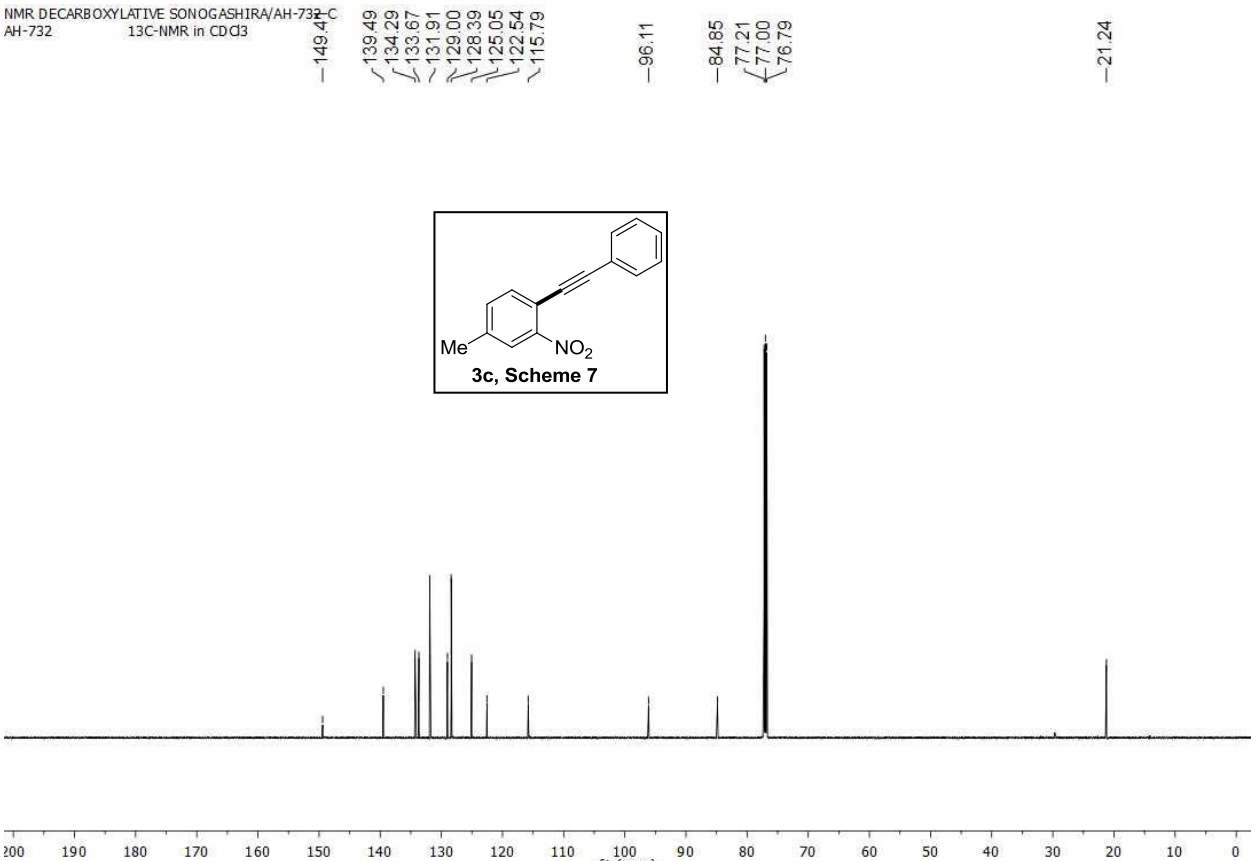

AH-727-C/1

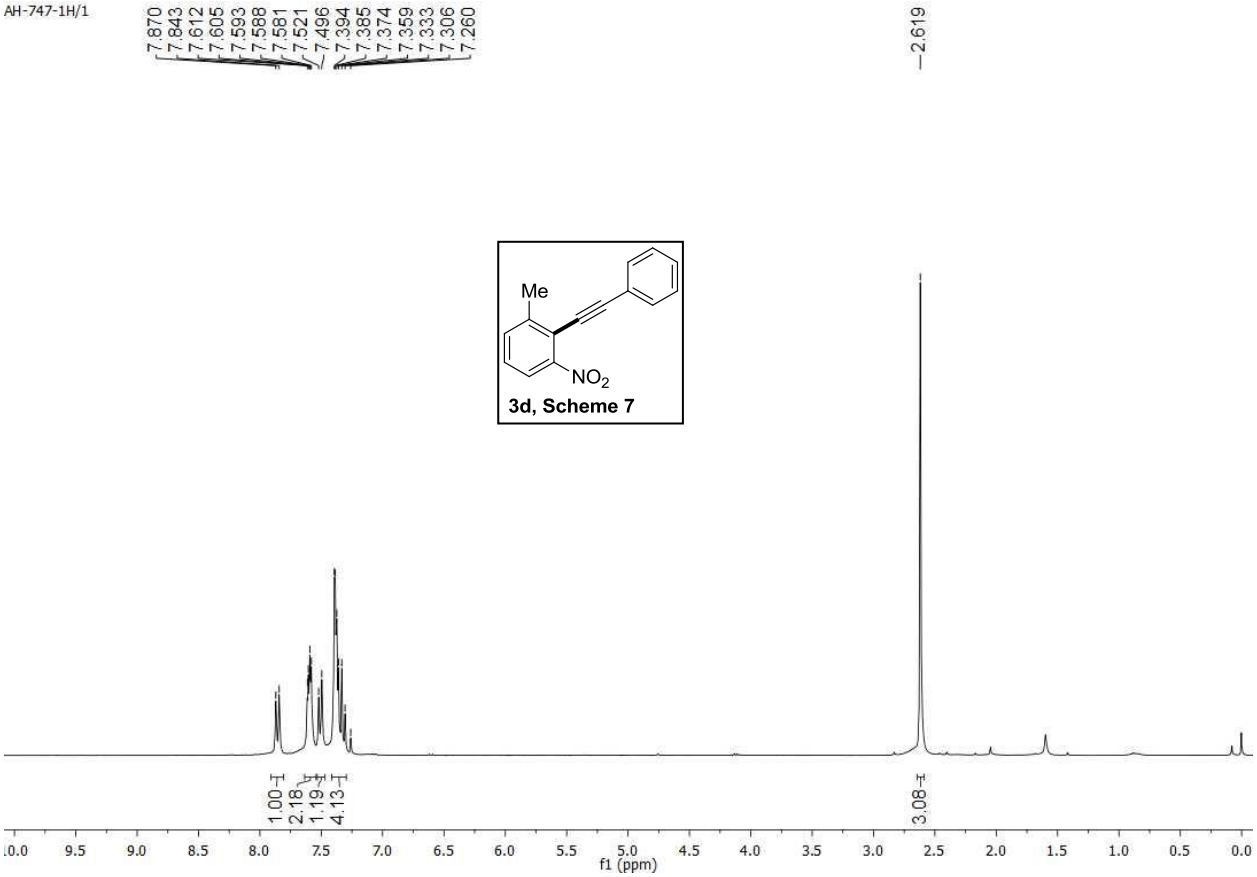




**3a, Scheme 7**




7.903
7.616
7.607
7.603
7.598
7.592
7.421
7.408
7.391
7.386
7.380
7.275
2.473
Me
NO2
3c, Scheme 7
1.00
3.13
1.12
3.18
3.15
f1 (ppm)


NMR DECARBOXYLATIVE SONOGASHIRA/AH-732-C
AH-732 13C-NMR in CDCl3
149.41
139.49
134.29
133.67
131.91
129.00
128.39
125.05
122.54
115.79
96.11
84.85
77.21
77.00
76.79
21.24
Me
NO2
3c, Scheme 7
f1 (ppm)


AH-747-1H/1
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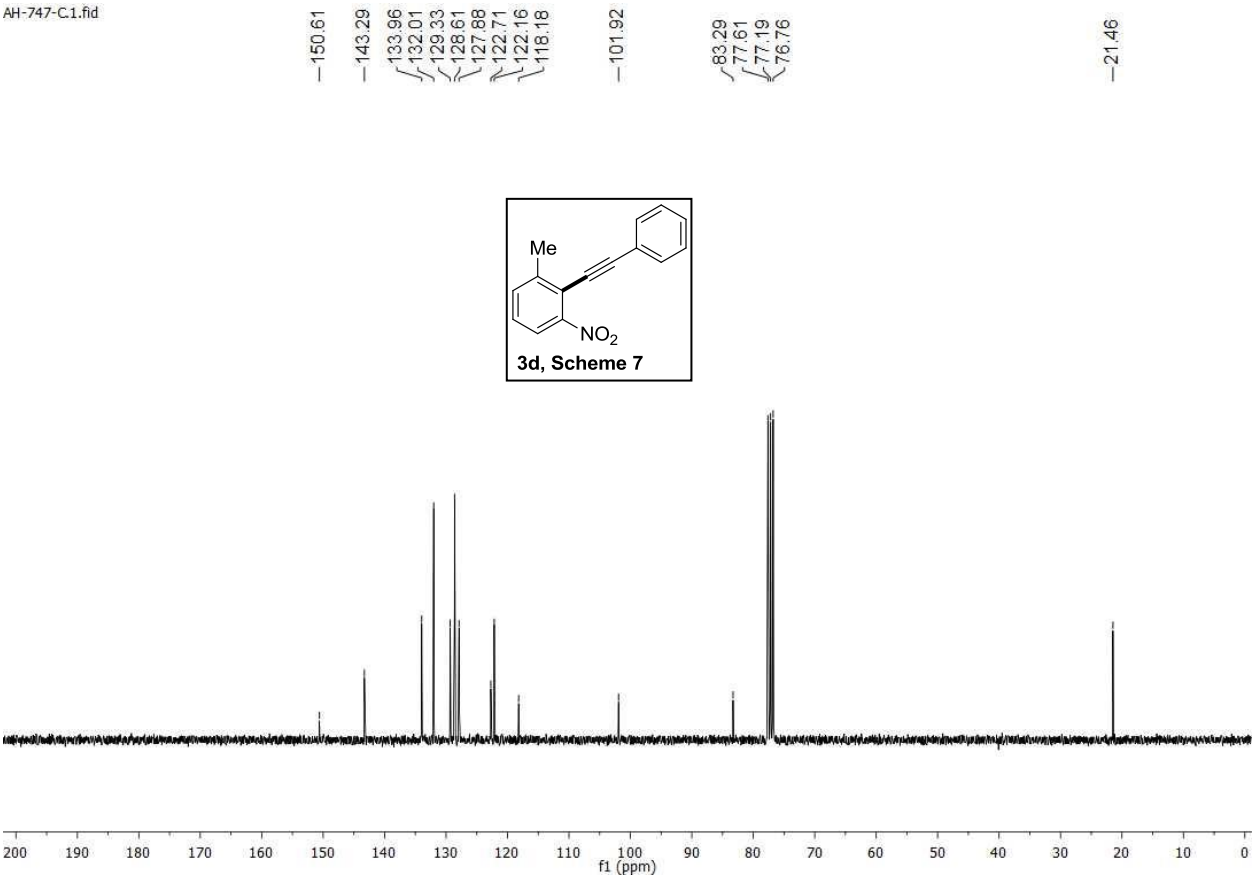
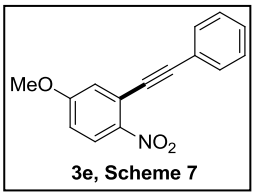
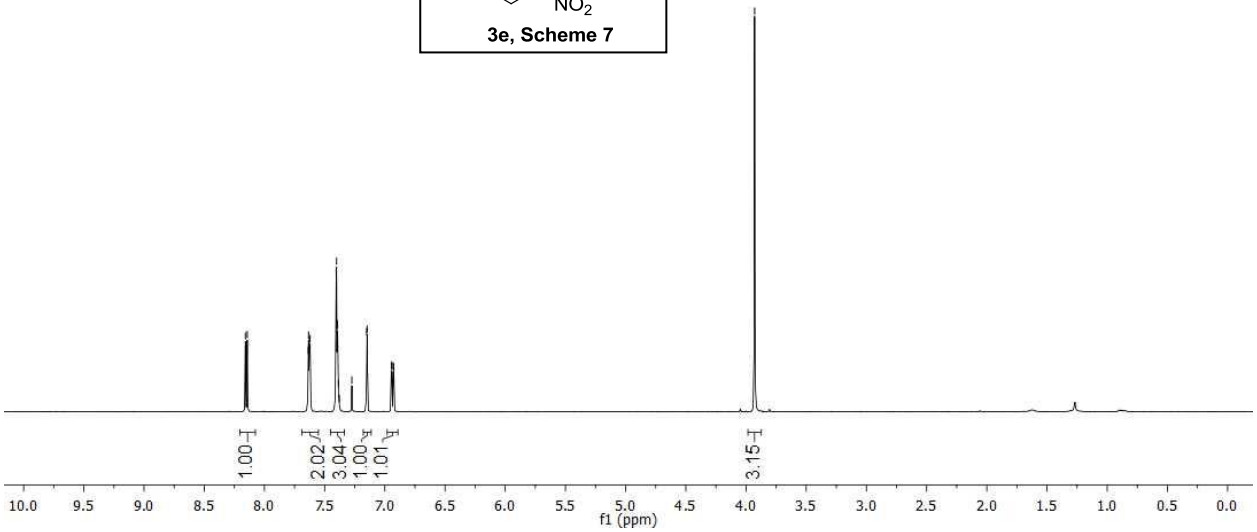
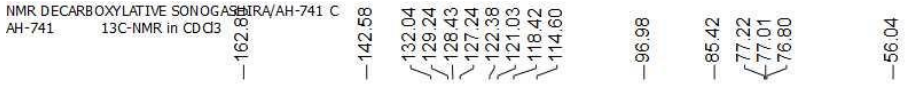
7.843
7.612
7.605
7.593
7.588
7.581
7.521
7.496
7.394
7.385
7.374
7.359
7.333
7.306
7.260
2.619
Me
NO2
3d, Scheme 7
1.00
2.18
1.19
4.13
3.08
f1 (ppm)

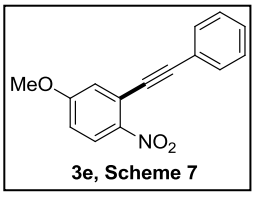

AH-747-C.1.fid
150.61
143.29
133.96
132.01
129.33
128.61
127.88
122.71
122.16
118.18
101.92
83.29
77.61
77.19
76.76
21.46
Me
NO2
3d, Scheme 7
f1 (ppm)

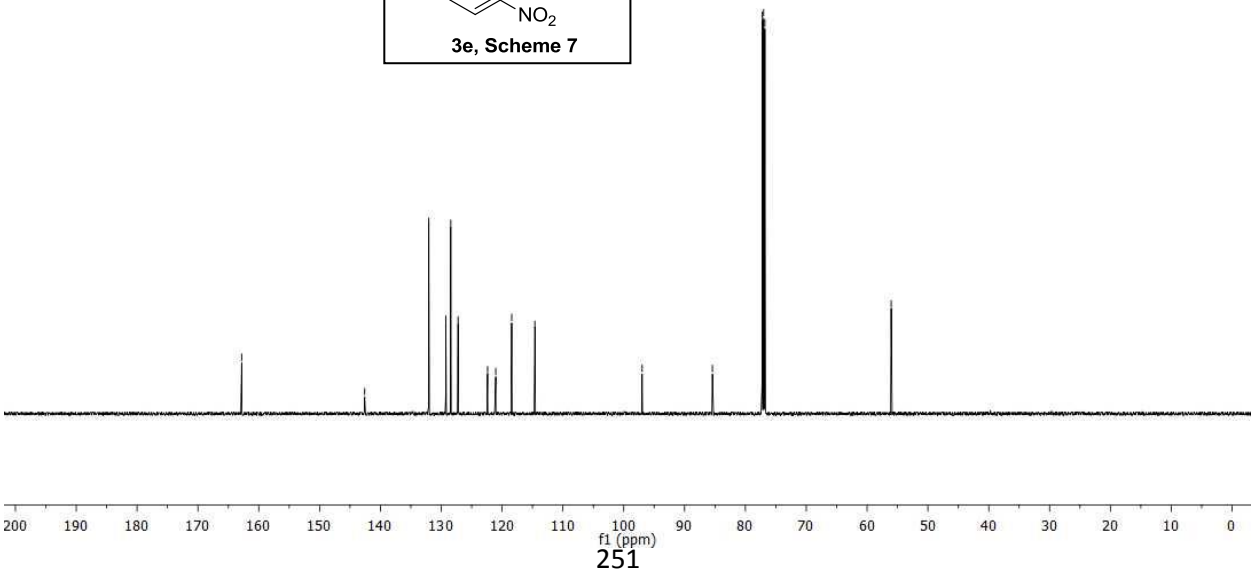

**3e, Scheme 7**



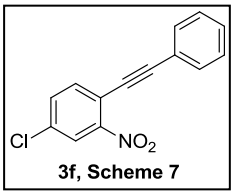



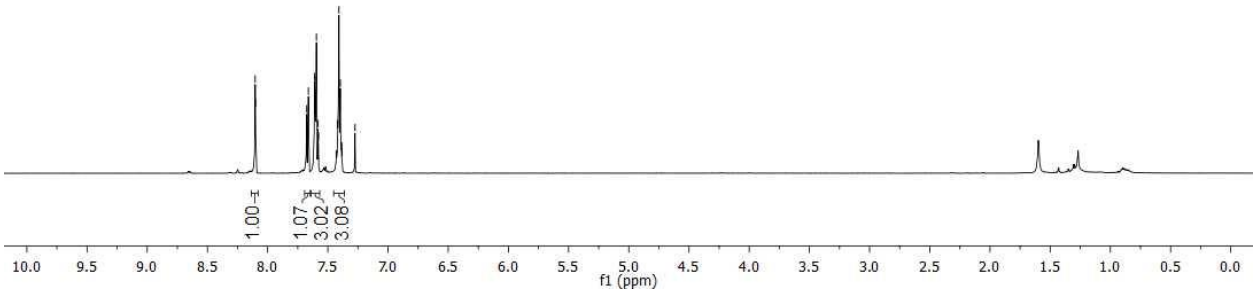



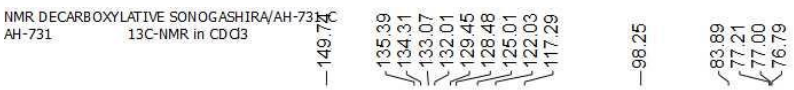

**3e, Scheme 7**

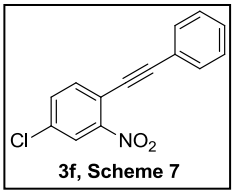



8.103
8.100
7.675
7.661
7.609
7.607
7.595
7.581
7.577
7.430
7.428
7.419
7.417
7.408
7.396
7.387
7.386
7.383
7.274

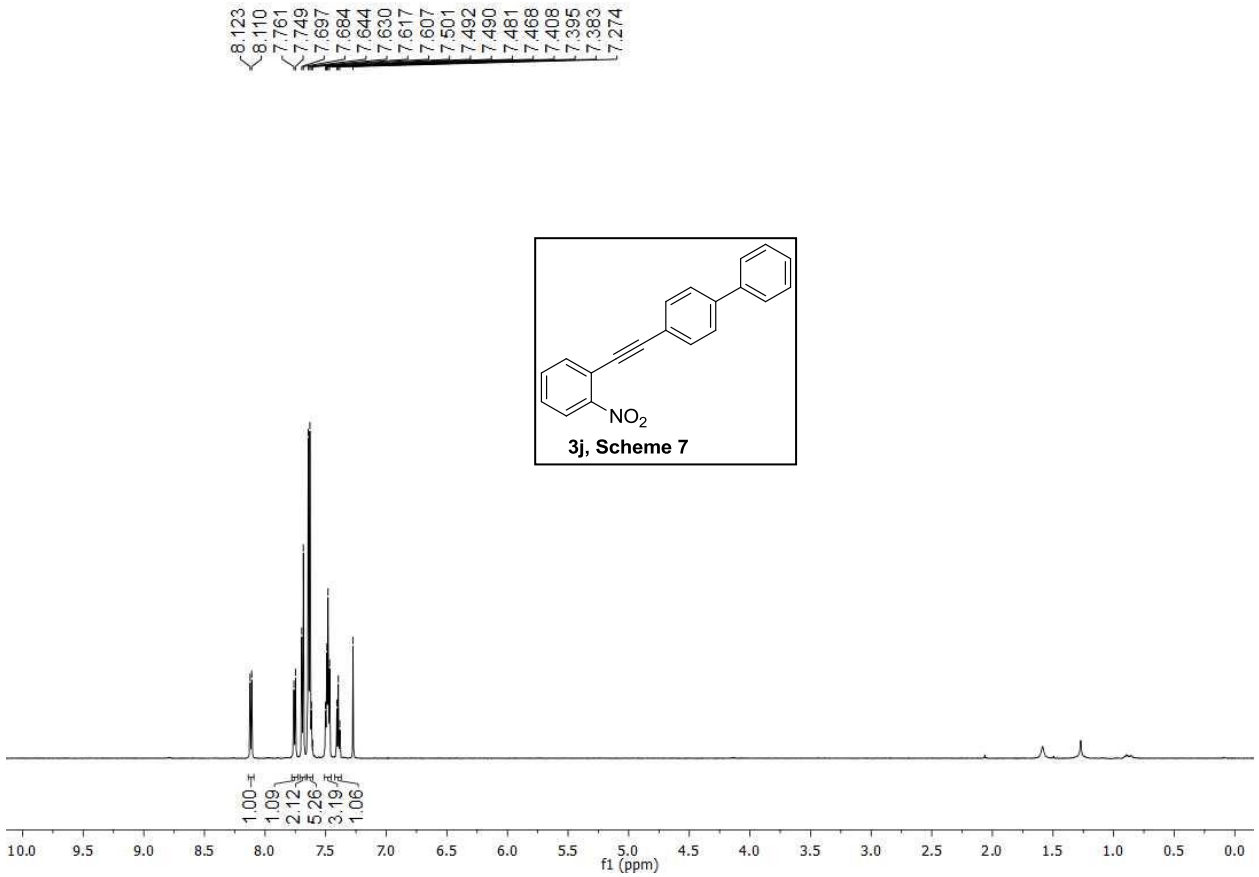

Cl
NO2
3f, Scheme 7

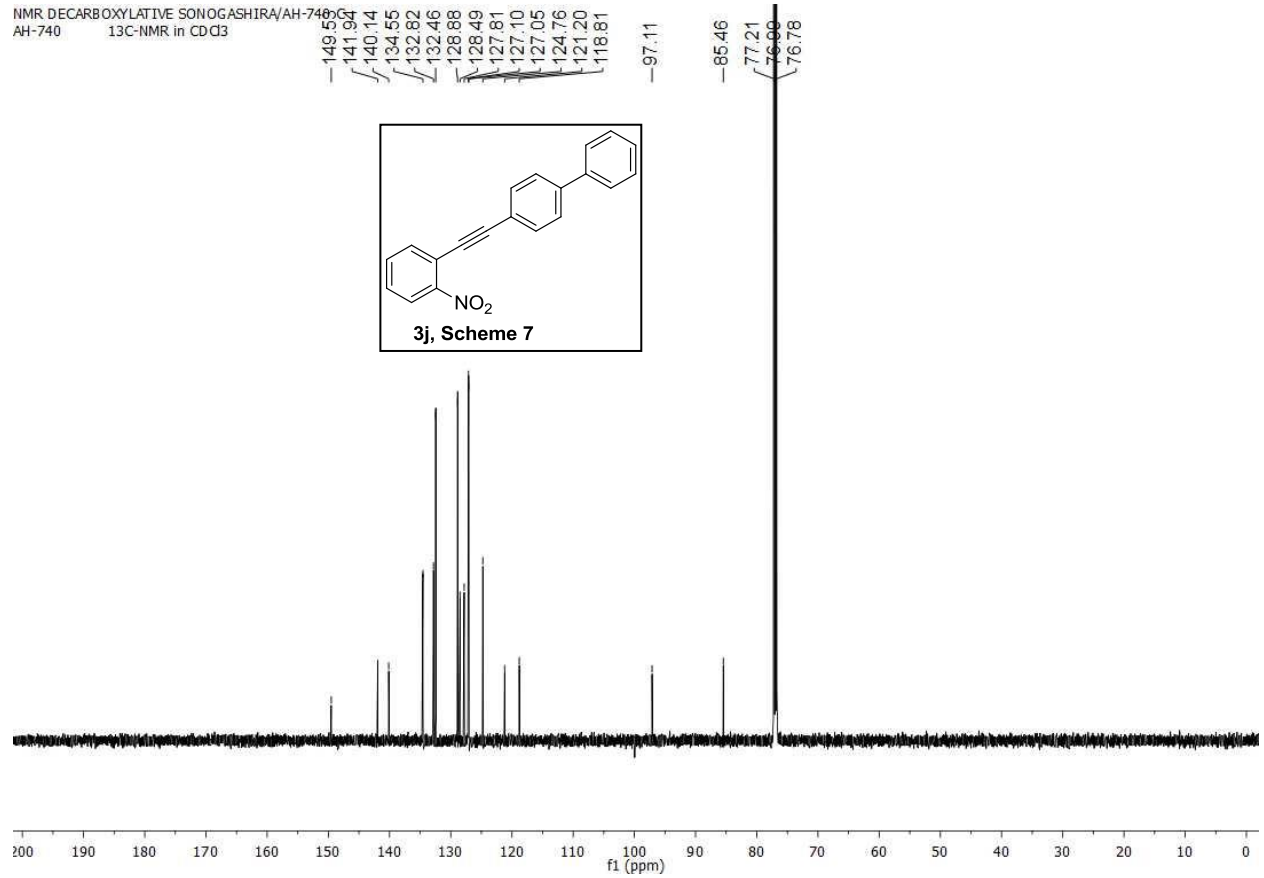

1.00
1.07
3.02
3.08
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

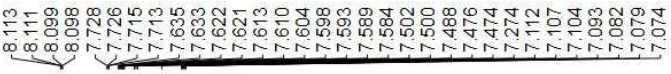

NMR DECARBOXYLATIVE SONOGASHIRA/AH-731-C
AH-731 13C-NMR in CDCl3
149.72
135.39
134.31
133.07
132.01
129.45
128.48
125.01
122.03
117.29
98.25
83.89
77.21
77.00
76.79

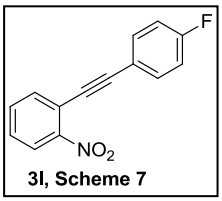

Cl
NO2
3f, Scheme 7


200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

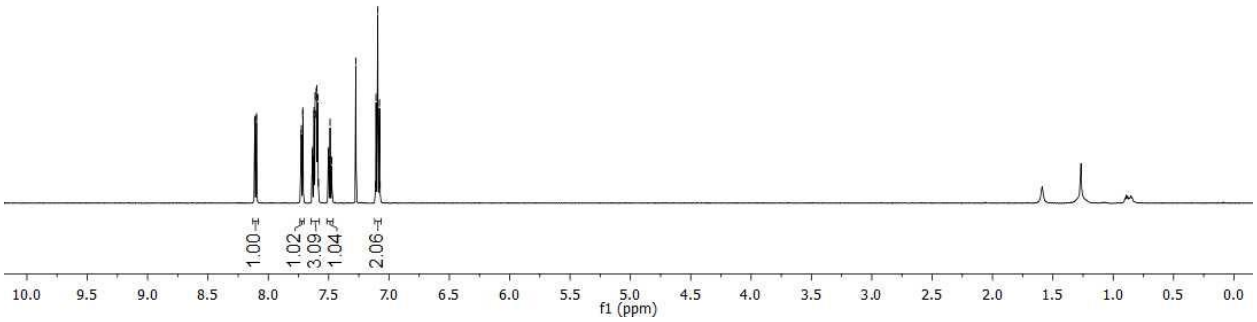

8.123
8.110
7.761
7.749
7.697
7.684
7.644
7.630
7.617
7.607
7.501
7.492
7.490
7.481
7.468
7.408
7.395
7.383
7.274
NO2
3j, Scheme 7
1.00
1.09
2.12
5.26
3.19
1.06
f1 (ppm)

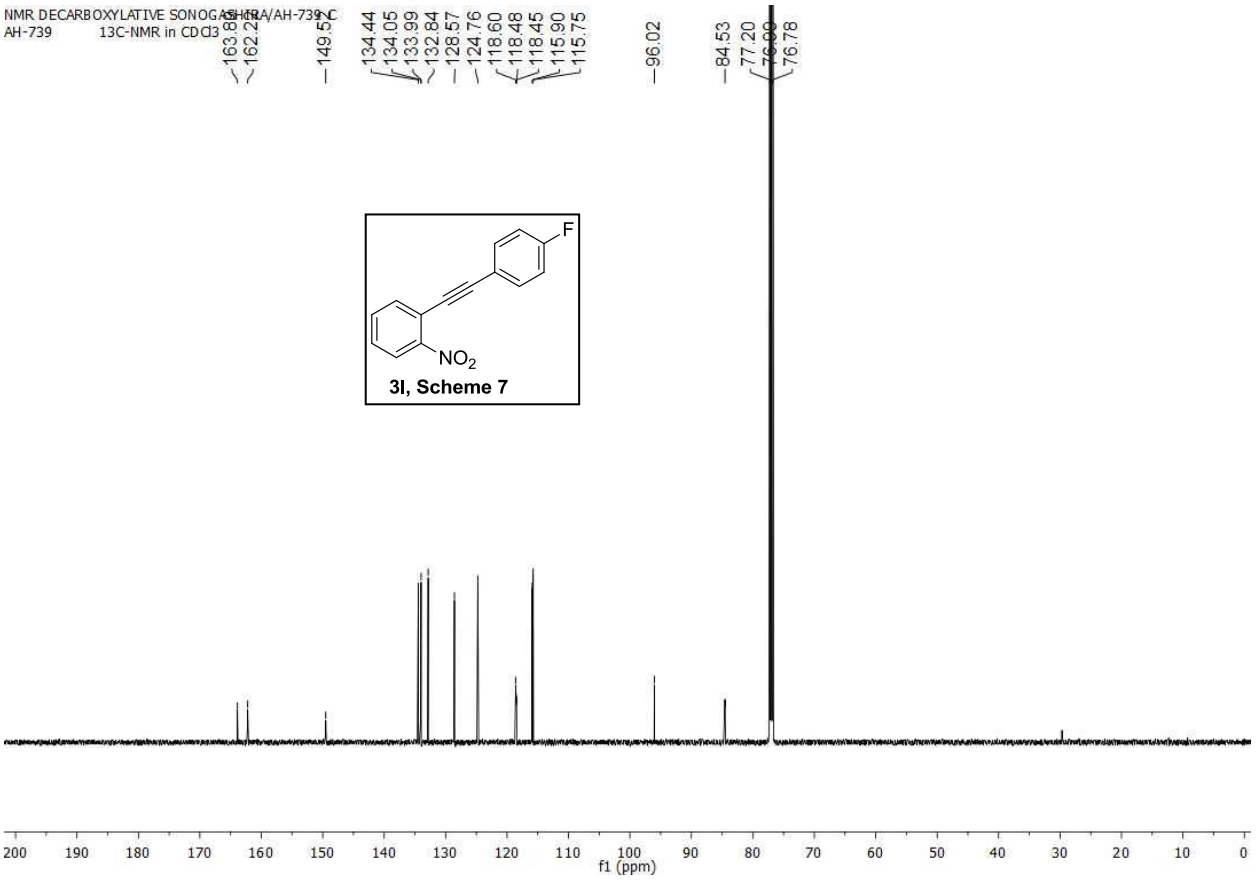

NMR DECARBOXYLATIVE SONOGASHIRA/AH-740-C
AH-740 13C-NMR in CDCl3
149.50
141.94
140.14
134.55
132.82
132.46
128.88
128.49
127.81
127.10
127.05
124.76
121.20
118.81
97.11
85.46
77.21
76.99
76.78
NO2
3j, Scheme 7
f1 (ppm)




**3l, Scheme 7**

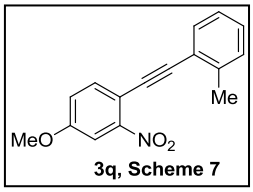


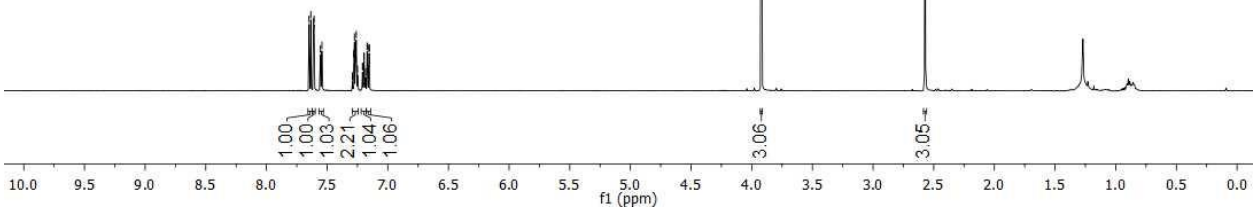



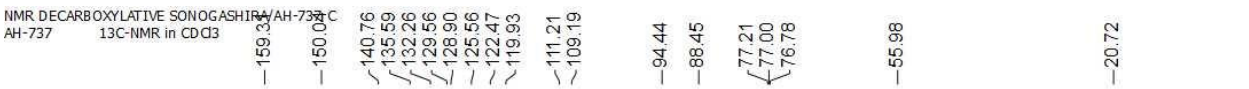

**3l, Scheme 7**

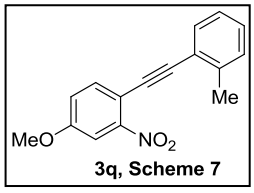

7.649
7.634
7.612
7.607
7.555
7.543
7.292
7.290
7.279
7.278
7.275
7.268
7.266
7.260
7.249
7.209
7.206
7.197
7.194
7.182
7.171
7.166
7.156
7.152


3.921
2.571

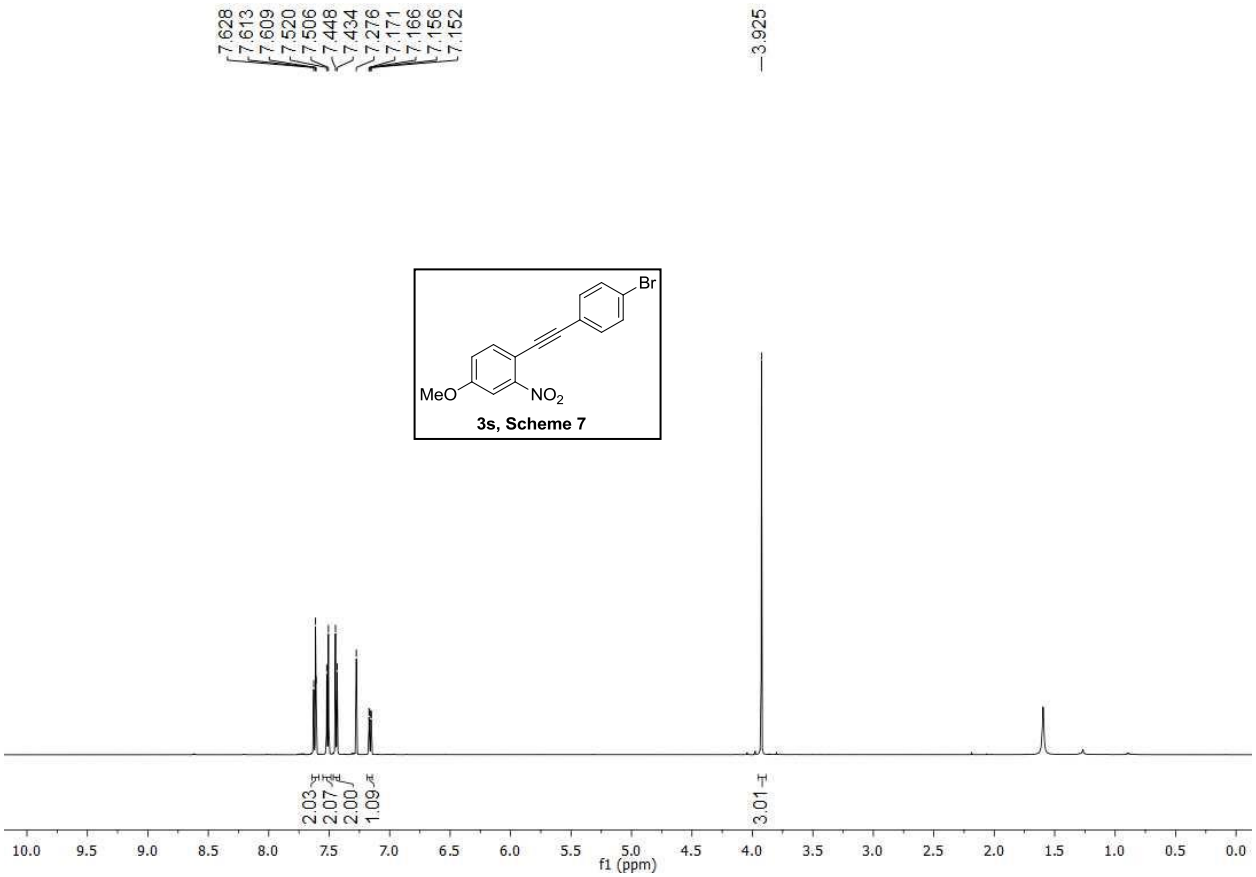

Me
MeO
NO2
3q, Scheme 7

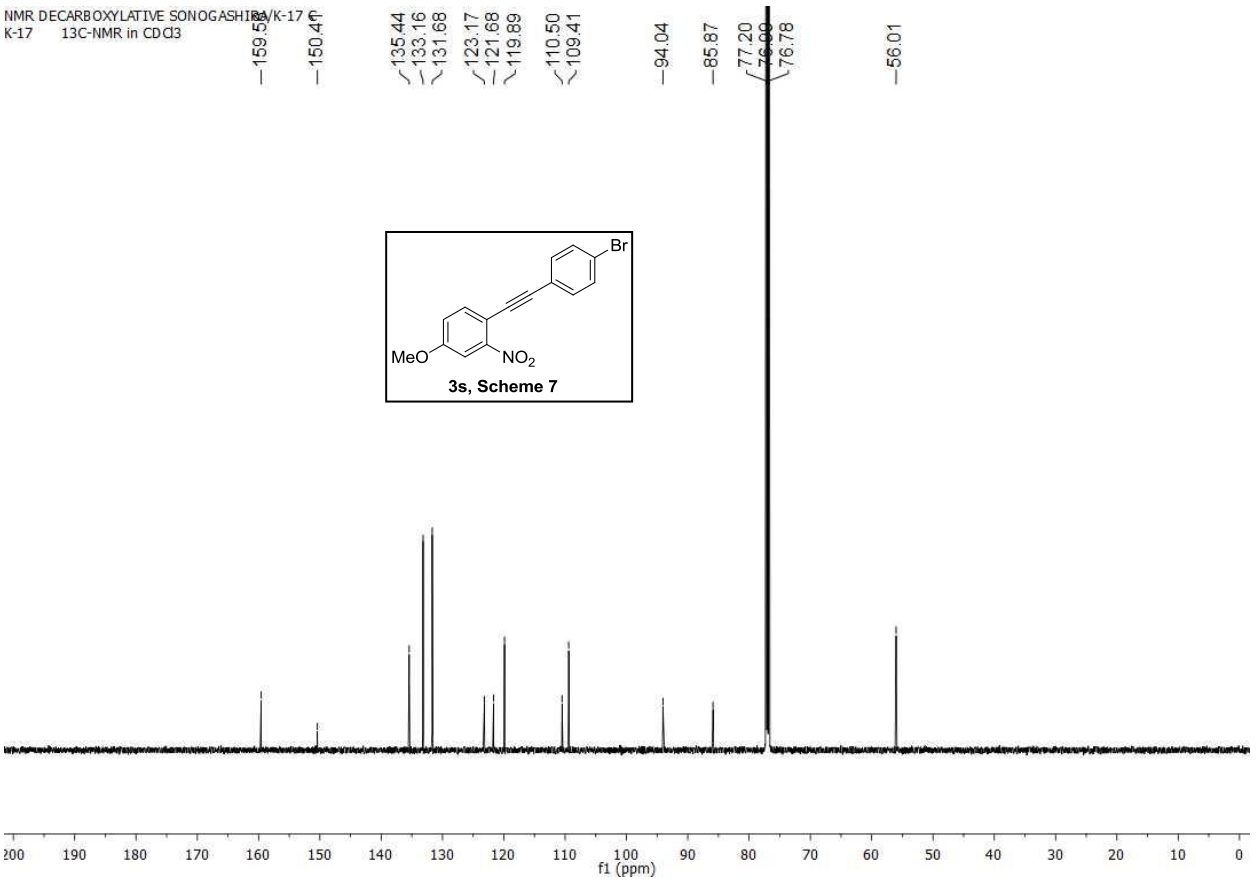

1.00
1.00
1.03
2.21
1.04
1.06
3.06
3.05
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


NMR DECARBOXYLATIVE SONOGASHIRA/AH-737-C
AH-737 13C-NMR in CDCl3
159.34
150.04
140.76
135.59
132.26
129.56
128.90
125.56
122.47
119.93
111.21
109.19
94.44
88.45
77.21
77.00
76.78
55.98
20.72


Me
MeO
NO2
3q, Scheme 7


200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

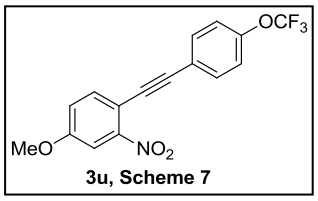

7.628
7.613
7.609
7.520
7.506
7.448
7.434
7.276
7.171
7.166
7.156
7.152
3.925
Br
MeO
NO2
3s, Scheme 7
2.03
2.07
2.00
1.09
3.01
f1 (ppm)


NMR DECARBOXYLATIVE SONOGASHIRA/K-17
K-17 13C-NMR in CDCl3
159.58
150.41
135.44
133.16
131.68
123.17
121.68
119.89
110.50
109.41
94.04
85.87
77.20
76.99
76.78
56.01
Br
MeO
NO2
3s, Scheme 7
f1 (ppm)

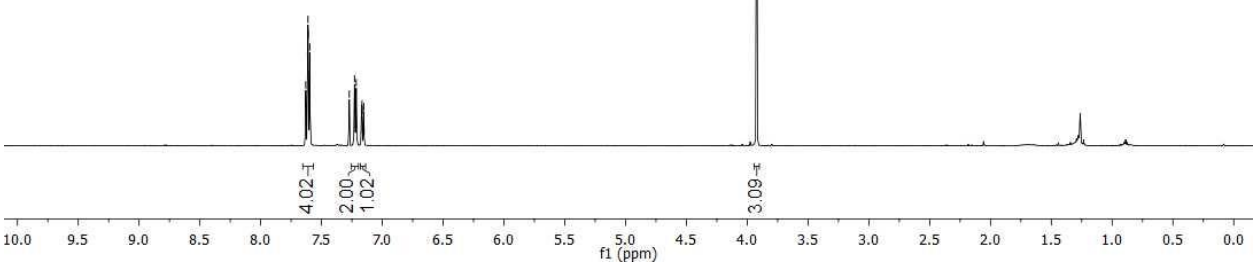
NMR DATA/AH-740A P
AH740 1H-NMR in CDCl3

7.630
7.627
7.615
7.611
7.609
7.600
7.597
7.272
7.229
7.215
7.171
7.167
7.164
7.157
7.153
7.150

3.922

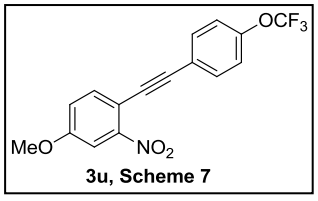



**3u, Scheme 7**




NMR DATA/AH-740A C
AH740 13C-NMR in CDCl3

159.62
150.46
149.24
135.46
133.31
122.88
121.49
121.17
120.87
119.86
119.46
117.75
110.39
109.42
93.58
85.55
77.20
76.99
76.77
56.00




**3u, Scheme 7**

## V. 9. References

(1) (a) Ketel, D. H. *Chemistry and Biology of Naturally-Occurring Acetylenes and Related Compounds*; Lam, J.; Breteler, H.; Arnason, T.; Hansen, L., Eds.; Elsevier, Amsterdam, 1988. (b) *Chemistry of Triple Bonded Functional Groups*; Patai, S., Ed.; Wiley-VCH, New York, 1994. (c) *Modern Acetylene Chemistry;* Stang, P. J.; Diederich, F., Eds.; Wiley-VCH, Weinheim, 1995. For reviews, see: (d) Liu, Y.; Lam, J. W. Y.; Tang, B. Z. *Nat. Sci. Rev*. **2015**, *2*, 493-509. (e) Jewett, J. C.; Bertozzi, C. *Chem. Soc. Rev*. **2010**, *39*, 1272-1279. (f) Thirumurugan, P.; Matasiuk, D.; Jozwiak, K. *Chem. Rev*. **2013**, *113*, 4905-4979.

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## List of Publications

(1) Palladium(0)-Catalyzed Intramolecular Decarboxylative Allylation of Ortho Nitrobenzoic Esters- **Hossian, A**.; Singha, S.; Jana, R. *Org. Lett*. **2014**, *16*, 3934-3937.

(2) Merging C-H Activation and Alkene Difunctionalization at Room Temperature: A Palladium-Catalyzed Divergent Synthesis of Indoles and Indolines- Manna, M. K.; **Hossian, A**.; Jana, R. *Org. Lett.* **2015**, *17*, 672-675.

(3) Chemo-, regio-, and stereoselective Heck-Matsuda arylation of allylic alcohols under mild conditions- Chaudhari, T. Y.; **Hossian, A**.; Manna, M. K.; Jana, R. *Org. Biomol. Chem.* **2015**, *13*, 4841-4845.

(4) Substrate-Dependent Mechanistic Divergence in Decarboxylative Heck Reaction at Room Temperature- **Hossian, A**.; Bhunia, S. K.; Jana, R. *J. Org. Chem*. **2016**, *81*, 2521-2533.

(5) Carboxyl radical-assisted 1,5-aryl migration through Smiles rearrangement- **Hossian, A**.; Jana, R. *Org. Biomol. Chem*. **2016**, *14*, 9768-9779.

(6) Palladium-Catalyzed Decarboxylative, Decarbonylative and Dehydrogenative C($sp^2$)-H Acylation at Room Temperature- **Hossian, A**.; Manna, M. K.; Manna, K.; Jana, R. *Org. Biomol.Chem.* **2017**, *15*, 6592-6603.

(7) $Cu^{I}$/$Ag^{I}$-Promoted Decarboxylative Alkynylation of ortho-Nitro Benzoic Acids- **Hossian, A**.; Manna, K.; Das, P.; Jana, R. *ChemistrySelect* **2018**, *3*, 4315-4318.

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# Palladium(0)-Catalyzed Intramolecular Decarboxylative Allylation of Ortho Nitrobenzoic Esters

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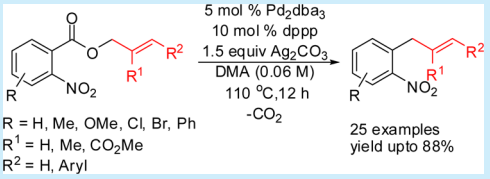
Supporting Information

**ABSTRACT:** A Pd/Ag bimetallic system has been developed for the decarboxylative allylation of *ortho*-nitrobenzoic esters in an intramolecular fashion. In contrast to the typical $sp^2-sp^3$ cross-coupling approach which requires air and moisture sensitive preformed organometallic reagents, we provide an alternative route to the synthesis of *ortho*-allyl nitroarenes from the corresponding *ortho*-nitrobenzoic acid derivatives. The reaction proceeds through a mechanistically distinct decarboxylative metalation pathway. A cooperative reactivity of palladium and silver is crucial for the reaction outcome.




Aromatic nitro compounds are useful intermediates for the synthesis of agrochemicals, pharmaceuticals, dyes, photoreactive compounds, high energetic materials, radiopharmaceutical tracers, etc.[1] A facile reduction of the aromatic nitro groups to their corresponding anilines provides common starting materials for the syntheses of a plethora of *N*-heterocycles and natural products.[2] Despite their interesting properties, access to *ortho*-substituted nitroarenes is limited due to inherent incompatibility with some organometallic reagents.[3] To overcome this problem the Knochel group introduced an elegant approach for the generation of nitro-containing organometallics via I−Mg exchange.[4] However, this protocol suffers from serious limitations such as the use of air and moisture sensitive preformed organometallic reagents, highly toxic copper(I)cyanide, and expensive organohalides. Therefore, alternative routes to the synthesis of *ortho*-functionalized nitroarenes using inexpensive, air and moisture stable starting materials are in high demand.

Recently, increasing use of nitrobenzoic acid derivatives in palladium-catalyzed decarboxylative cross-coupling reactions[5] has also motivated us to explore the *ortho*-allylation reaction. Although palladium-catalyzed decarboxylative $sp^3-sp^3$ allylic alkylation has been widely explored,[6] decarboxylative $sp^2-sp^3$ allylation is less studied.[7] In this vein, an activated coumarin moiety furnished moderate to good yields of allylation product and preferred $sp^3-sp^3$ allylation[6i] over the $sp^2-sp^3$ allylation.[7a] Decarboxylative allylation of electron-rich arenes also provided poor yields of the desired products.[7b] Decarboxylative allylation of $\alpha$-oxocarboxylates resulted in $\alpha,\beta$-unsaturated ketones through alkene isomerization.[7c] The difficulty in decarboxylative $sp^2-sp^3$ allylation arises due to the fact that, in $sp^3-sp^3$ allylation, the incipient anion after decarboxylation is stabilized by the proximal electron-withdrawing groups such as keto,[8] ester,[9] nitro,[10] cyano,[11] sulfone,[12] etc. Whereas, in the case of $sp^2-sp^3$ allylation, the anion on the $sp^2$-carbon is highly unstable and exhibits a high propensity toward protonation. Therefore, selective $sp^2-sp^3$ decarboxylative allylation in high yields is an extremely challenging task to achieve. To our surprise, decarboxylative $sp^2-sp^3$ allylation of electron-deficient arenes especially nitroarenes is not known. We hypothesized that the nitro group at the *ortho* position could be beneficial in decarboxylative allylation as it can stabilize the aryl anion which is formed after decarboxylation.

We started optimization of the reaction conditions by heating a mixture of *ortho*-nitrobenzoic acid and allyl bromide and a catalytic amount of Pd(0) at 160 °C, but no allylation product was formed. Switching to allyl acetate from allyl bromide resulted in a trace amount of allylation product along with nitrobenzene as a major product. We realized that the carboxylic acid proton could be detrimental for the allylation product formation and may lead to the undesired protonation product. Therefore, the potassium salt of the corresponding nitrobenzoic acid was employed, but unfortunately, no allylation product was observed. Next, an allyl ester of the corresponding acid was prepared and subjected to the intramolecular decarboxylative allylation (Table 1). Interestingly, all starting material was consumed and a mixture of corresponding allyl and styrenyl products was isolated in slightly improved yield (entry 18, Table 1). Still, the undesired *ortho*-nitrobenzoic acid and nitrobenzene were formed predominantly. The poor mass balance toward the allylation product can be attributed due to decomposition of the $\pi$-allyl-Pd species[13] and double bond isomerization at elevated temperature to generate the undesired styrenyl product. Therefore, we decided to use the silver(I) salt as an additive since it is known to promote decarboxylation at lower temperature[14] and decreases double bond isomerization.[15] Gratifyingly, yield was improved to 55% with the addition of only 10 mol % of the silver carbonate (entry 5, Table 1). After a rigorous study varying the catalyst, ligand, solvent, and the

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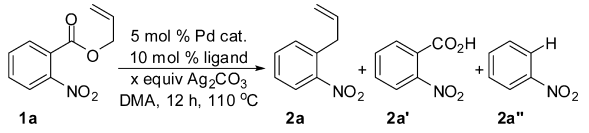
**Table 1. Optimization of the Reaction Conditions**[a]



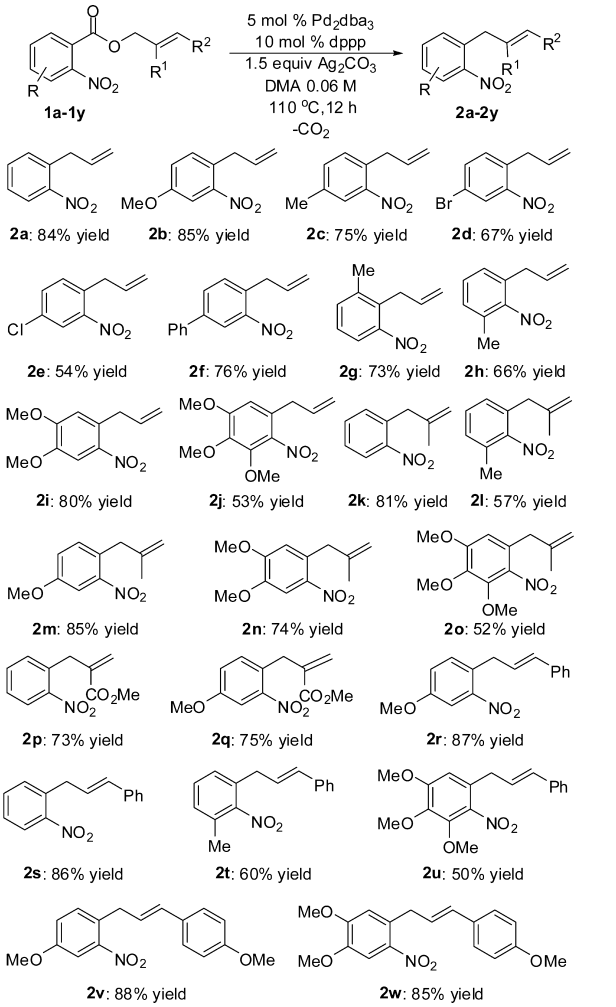

| entry | Pd cat. | ligand | $x$ | yield (%)[b] | 2a:2a′:2a″[b] |
|---|---|---|---|---|---|
| 1[c] | $Pd(PPh_3)_4$ | – | 0 | 0 | – |
| 2[c] | $Pd(PPh_3)_4$ | – | 0.2 | 30 | 70:10:20 |
| 3[c] | $Pd(OAc)_2$ | – | 0.2 | 0 | – |
| 4[c] | $Pd(tfa)_2$ | – | 1.5 | 0 | – |
| 5 | $Pd_2dba_3$ | xantphos | 0.1 | 55 | 80:7:13 |
| 6 | $Pd_2dba_3$ | dppf | 0.1 | 50 | 75:10:15 |
| 7 | $Pd_2dba_3$ | rac-BINAP | 0.1 | 63 | 73:7:20 |
| 8 | $Pd_2dba_3$ | dppp | 0.1 | 68 | 82:10:8 |
| 9 | $Pd_2dba_3$ | dppp | 0.5 | 72 | 85:6:9 |
| 10 | $Pd_2dba_3$ | dppp | 1.0 | 80 | 85:5:10 |
| **11** | **$Pd_2dba_3$** | **dppp** | **1.5** | **90** | **94:0:6** |
| 12 | $Pd_2dba_3$ | dppp | 2.0 | 88 | 92:0:8 |
| 13 | $Pd_2dba_3$ | dppe | 1.5 | 40 | 78:13:9 |
| 14 | $Pd_2dba_3$ | dppb | 1.5 | 50 | 80:12:8 |
| 15 | $Pd_2dba_3$ | $PCy_3$ | 1.5 | 45 | 82:10:8 |
| 16 | $Pd_2dba_3$ | xphos | 1.5 | 60 | 77:13:10 |
| 17[d] | $Pd_2dba_3$ | dppp | 0 | 0 | – |
| 18[e] | $Pd_2dba_3$ | dppp | 0 | 55 | 30:43:27 |
| 19 | $Pd(tfa)_2$ | dppp | 1.5 | 48 | 63:27:10 |
| 20[f] | $Pd(tfa)_2$ | – | 3.0 | 7 | – |

[a]All reactions were carried out in 0.1 mmol scale, in DMA 0.06 M. [b]Yields refered to here are overall isolated yields, and product distributions were determined by $^1$H NMR of the crude product. [c]10 mol % of the Pd cat. was used. [d]100 mol % of the $Pd_2dba_3$ and 200 mol % of the dppp were used. [e]The reaction was heated at 160 °C; a mixture of allyl and styrenyl product was isolated. [f]20 mol % of $Pd(tfa)_2$, DMF/DMSO (19:1), 120 °C.

amount of additive, the allylation product was isolated in excellent yields using a combination of 5 mol % $Pd_2dba_3$, 10 mol % dppp with 1.5 equiv of $Ag_2CO_3$ in DMA at 110 °C.

Under the optimized reaction conditions, we explored the substrate scope for the decarboxylative allylation reaction (Scheme 1). A variety of substituted nitroarenes allow the formation of allylation products in good to excellent yields. A careful study revealed that electron-donating substituents such as *p*-OMe on *o*-nitrobenzoate favor allylation product formation (**2b**, **2m**, **2q**, **2r**, **2v**, Scheme 1) and two *m*-OMe groups which are electron-withdrawing in nature lower the yields to some extent (**2i**, **2n**, **2w**, Scheme 1). However, yields of the allylation products are decreased drastically with a substitution of three adjacent −OMe groups due to low conversion, substantial amounts of protonation product, and carboxylic acid formation (**2j**, **2o**, **2u**, Scheme 1). Substrates with an electron-deficient substituent, e.g. 2,4-dinitro benzoic ester, resulted in a decarboxylative protonation product only. Therefore, electron-withdrawing substituents on the *o*-nitro-benzoate facilitate decarboxylation but they decrease the ability of the aryl anion to serve as a $\sigma$-donor for the Pd(II)allyl cation. Halogen substituents, such as Br, Cl, are compatible with the reaction conditions (**2d**, **2e**, Scheme 1) which may undergo further cross-coupling reactions. In addition to the cross-couplings of unsubstituted allyl esters, a variety of substituted and functionalized allyl esters also underwent couplings to provide allylation products (**2k**−**2q**, Scheme 1). Allyl esters from the corresponding cinnamyl alcohols and its derivatives produced

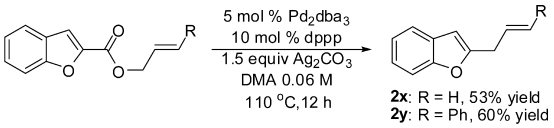
**Scheme 1. Substrate Scope of Decarboxylative Allylation**[a,b]




[a]All reactions were carried out in 0.3 mmol scale. [b] Yields refer to the average of isolated yields of at least two experiments.

the linear product selectively (**2r**−**2w**, Scheme 1). However, allyl esters that possess $\beta$-hydrogens such as crotyl, prenyl, 2-cyclohexenyl esters preferentially formed conjugated dienes via $\beta$-hydrogen elimination and a protonation product[6g] (see Supporting Information, Scheme 1). A selective reduction of the nitro group afforded *o*-allyl aniline in excellent yields (Supporting Information, Scheme 2).

**Scheme 2. Decarboxylative Allylations of Benzofuran-2-Carboxylates**




Subsequently, several heteroaromatic carboxylic esters were tested under the reaction conditions. Unfortunately, nitrogen-containing heterocycles such as indole and pyridine-2-carboxylic esters did not furnish any desired product. However, benzofuran-2-carboxylic esters furnished an allylation product in good to moderate yields (Scheme 2).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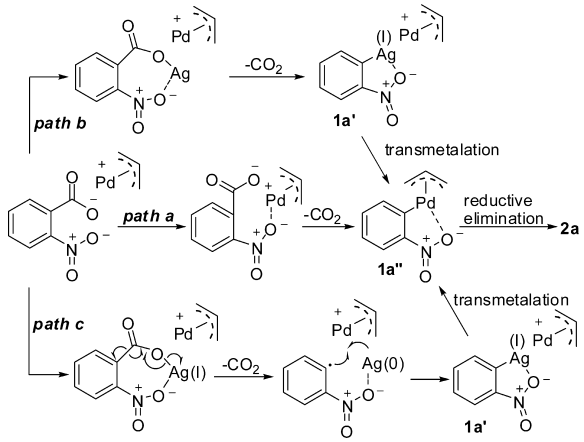
Next, we turned our attention toward gaining insight into the reaction mechanism. After oxidative addition of palladium(0) to the allyl ester **1a** the reaction may proceed in three distinct pathways. In ***path a***, the solvent-separated ion pair may undergo decarboxylation via a two-electron process[16] followed by carbopalladation to generate **1a**″ which is converted to the desired product after reductive elimination. Whereas, in ***path b***, a silver-assisted decarboxylation via an anionic route can generate the arylsilver species **1a**′ which can undergo transmetalation with palladium followed by reductive elimination to furnish an allylation product. Alternatively, this silver-assisted decarboxylation may proceed via a Hunsdiecker-type free radical pathway as depicted in ***path c*** (Scheme 3). The *ortho*-nitro group can stabilize to either the organosilver(I) or organopalladium(II) prior to and after decarboxylation through coordination.

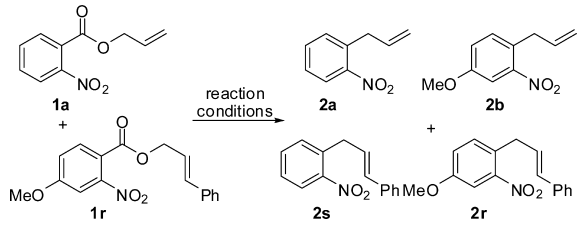
**Scheme 3. Possible Mechanistic Pathways**




To elucidate, several control experiments were performed. Heating the reaction mixture at 110 °C without any silver salt resulted in only nitrobenzoic acid. Even a stoichiometric amount of palladium also failed to promote decarboxylation at this temperature (entry 17, Table 1), whereas heating the reaction mixture at 160 °C with a catalytic amount of palladium afforded the desired product albeit in low yield (entry 18, Table 1). On the other hand, when *ortho*-nitro benzoic acid was heated at 110 °C only with the silver carbonate the nitrobenzene was formed indicating silver-assisted decarboxylation. To elucidate further, the reaction was carried out under the standard reaction conditions in the presence of 1.0 equiv of TEMPO, a radical scavenger. Almost the same yield of **2a** as under the standard conditions (84%) was obtained, which rules out the radical mechanism as shown in ***path c***. When Pd(II)/Ag(I) was used in lieu of Pd(0)/Ag(I), only starting material was recovered which indicates that Pd(0) is essential to initiate the reaction (entry 20, Table 1). An extensive crossover was also observed between two structurally disparate allyl esters, which is supportive evidence that the solvent-separated ion pairs are formed and undergo all possible combinations to provide the crossover products (Scheme 4).

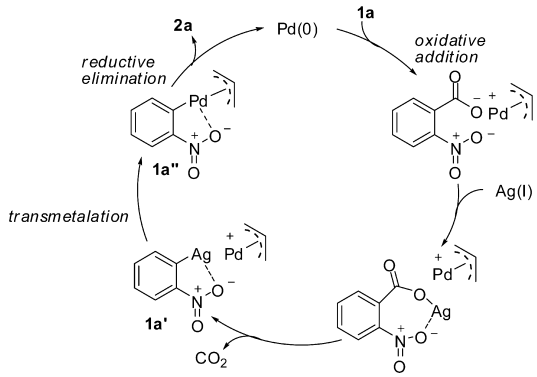
Based on these observations, we presumed that the reaction may proceed through ***path a*** at an elevated temperature vs ***path b*** under a Pd/Ag bimetallic system at a lower temperature. Initially, palladium(0) undergoes an oxidative addition to the allyl ester **1a** to form a $\pi$-allyl-Pd complex and an *ortho*-nitrobenzoate anion. Subsequently, a silver salt of the

**Scheme 4. Crossover Experiment**



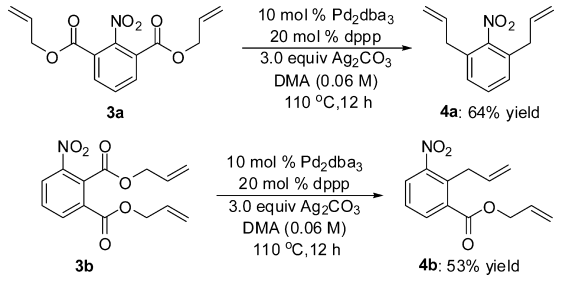

corresponding *ortho*-nitrobenzoic acid may form and undergo Ag(I)-assisted decarboxylation to afford the corresponding aryl-Ag species **1a**′. A transmetalation between an aryl-Ag and $\pi$-allyl-Pd complex generates an aryl-Pd species **1a**″. Finally, reductive elimination yields the desired allylation product and the Pd(0) to complete the catalytic cycle (Scheme 5).

**Scheme 5. Plausible Catalytic Cycle for the Decarboxylative Allylation**




Finally, to demonstrate the role of the nitro group in decarboxylative allylation, we synthesized diallyl ester **3a** where both ester groups are *ortho* to the nitro group and its corresponding regioisomer **3b** where one allyl ester group is at the *ortho* position and the other one is at the *meta* position. Under slightly modified reaction conditions, **3a** afforded a diallylation product in good yield via double decarboxylative allylations, whereas **3b** afforded the monoallylation along with the decarboxylative protonation product at the *ortho* position leaving the *meta* allyl ester intact (Scheme 6). Similarly, *para*-nitro benzoic ester was inactive under the reaction conditions. Presumably, the nitro group at the *ortho* position has a dual role in decarboxylation. First, it can coordinate to either the Ag(I) or Pd(II) prior to and after decarboxylation. This is particularly important for "post-decarboxylation" acting as a C/O bidentate

**Scheme 6. Selective Decarboxylative Allylation of Nitro Benzoic Esters**





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ligand to form a relatively stable 5-membered palladacycle. Second, it imparts a strong inductive effect that stabilizes the incipient anion which leads to rapid decarboxylation followed by allylation.

In conclusion, we have developed a Pd/Ag bimetallic system for the decarboxylative $sp^2$–$sp^3$ allylation of *ortho*-nitrobenzoic esters in an intramolecular fashion. A synergistic effect of palladium and silver was observed in this decarboxylative allylation. Mechanistic studies suggest that silver-assisted decarboxylation occurs in an anionic pathway at the presented reaction conditions which lead to an allylation product via transmetalation and reductive elimination.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures, spectroscopic data, $^1H$ and $^{13}C$ NMR spectra for all synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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# Substrate-Dependent Mechanistic Divergence in Decarboxylative Heck Reaction at Room Temperature

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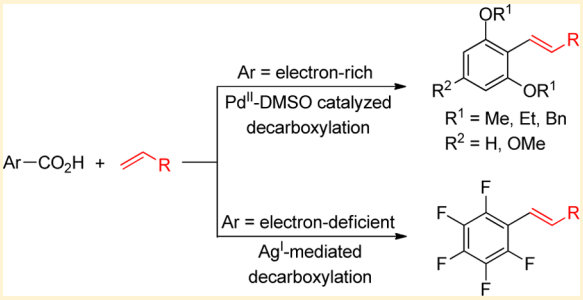
Supporting Information

**ABSTRACT:** We report herein a Pd(II)-catalyzed Heck-type coupling between arene carboxylic acids and alkenes at room temperature. Mechanistically, the reaction proceeds in two distinct pathways where electron-rich substrates undergo a palladium(II)-catalyzed decarboxylation and electron-deficient substrates proceed through silver(I)-assisted decarboxylation. Dimethyl sulfoxide (DMSO) or sulfide ligands have positive and negative roles in the reaction outcome, respectively. The present protocol is combined for the peptide modification under mild reaction conditions.




## INTRODUCTION

The decarboxylative cross-coupling of arene carboxylic acids with olefins and aryl electrophiles provides an attractive approach for the alkene functionalization and biaryl synthesis.[1] Inexpensive and readily available carboxylic acid as nucleophilic coupling partner is a user-friendly alternative to the air and moisture sensitive organometallic reagents. In a seminal report in 2002, Myers and co-workers reported a decarboxylative Heck-type olefination of arene carboxylic acids.[2] However, one of the major pitfalls in decarboxylative cross-coupling is the requirement of high reaction temperature (120−190 °C) which restricts its application in the synthesis of complex molecular frameworks. Because of the prevalence of stilbenes in numerous natural product, bioactive molecules and high tech materials (Figure 1),[3] we were particularly interested to the development of decarboxylative Heck-type coupling at room temperature.

Although, palladium-catalyzed decarboxylative coupling of nitroalkanes[4] and α-ketocarboxylic acids[5] at room temperature is known, there is no report of decarboxylative cross-coupling of arene carboxylates at room temperature. We report here for the first time a palladium-catalyzed decarboxylative Heck-type coupling at room temperature (Scheme 1). We also report the substrate-dependent mechanistic variation and distinct role of dimethyl sulfoxide/sulfide ligands in the present transformation.

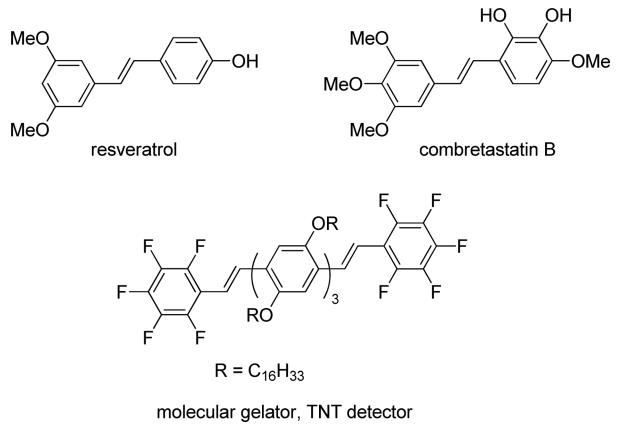



**Figure 1.** Representative example of some important stilbenes.

## RESULTS AND DISCUSSION

From literature it was evident that *o,o′*-disubstitution facilitates carbon dioxide extrusion.[6] In addition, from our previous experience with the decarboxylative allylation of *ortho*-nitrobenzoic acids, we realized that the incipient anion which is generated after decarboxylation needs to be stabilized for further cross-couplings.[7] Thus, we rationalized that either 2,6-dimethoxy benzoic acid or pentafluorobenzoic acid could be model substrates to study room temperature decarboxylative cross-coupling which will be a major advancement in this field.

Initially, we started screening for decarboxylative Heck reaction between 2,6-dimethoxybenzoic acid and styrene under the Myers's original conditions. But a trace amount of corresponding Heck product was isolated at room temperature. However, a good yield of the coupling product was isolated after 36 h stirring. In search for alternative oxidants to stoichiometric silver carbonate, 1,4-benzoquinone (BQ) was found to be suitable.[8] Finally, an excellent yield of the stilbene product was obtained after stirring the reaction mixture for 36 h

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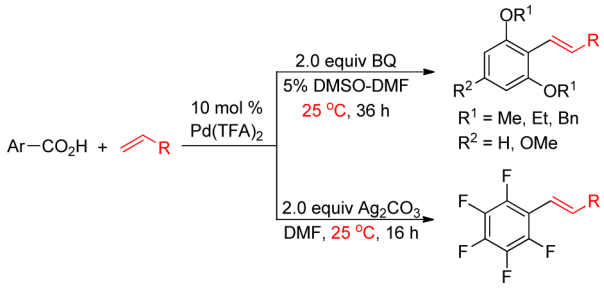
**Scheme 1. Decarboxylative Heck-Arylation with Olefins**

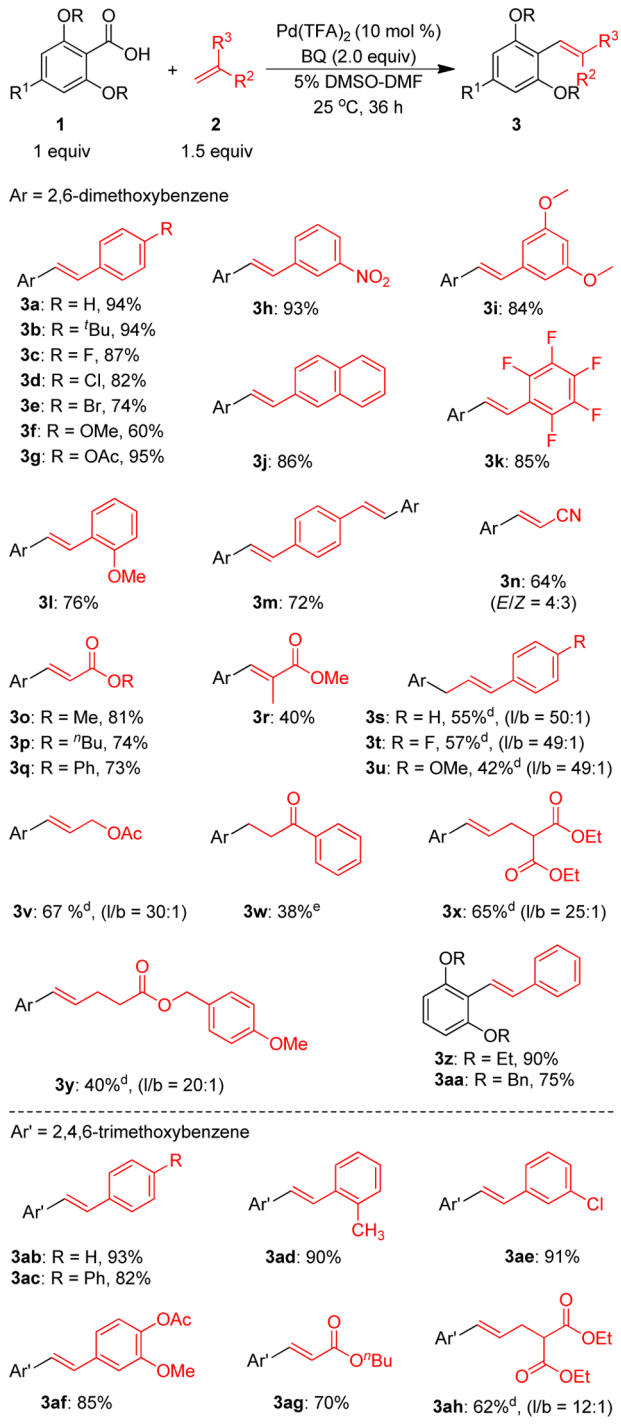



at room temperature with 10 mol % palladium catalyst and 2.0 equiv of 1,4-benzoquinone.

Being encouraged, several alkene partners were examined. A wide variety of styrenes having electron-withdrawing and electron-donating substituents underwent decarboxylative coupling providing high to excellent yields (Scheme 2). Fluoro-, chloro-, bromo-, (**3c**−**3e**, **3t**, **3ae**, Scheme 2) and remarkably acetoxy- (**3g**, **3af**, Scheme 2) groups were intact under the reaction conditions demonstrating the mild nature of this present protocol. Besides styrenes, activated alkenes such as acrylonitrile, (**3n**, Scheme 2) acrylates (**3o**−**3r**, **3ag**, Scheme 2) also provided the corresponding cross-coupling products. Interestingly, unactivated allylbenzenes (**3s**−**3u**, Scheme 2), allyl acetate (**3v**, Scheme 2), allyl malonate (**3x**, **3ah**, Scheme 2), and unactivated terminal alkene (**3y**, Scheme 2) also afforded the corresponding coupling products in good to moderate yields and good styrenyl selective products under slightly higher catalyst loading. The Heck coupling with an allyl alcohol (**3w**, Scheme 2) provided the corresponding ketone product via selective $\beta$-hydride elimination in moderate yield.[6b] Remarkably, 1,4-divinylbenzene provided the double cross-coupling product in one stroke (**3m**, Scheme 2). 2,6-Diethoxy- (**3z**, Scheme 2) and 2,6-dibenzyloxy (**3aa**, Scheme 2) benzoic acid also provided the corresponding coupling products in excellent yields. However, benzoic acid, mesitylenecarboxylic acid, 2-methoxy benzoic acid, and heteroaryl carboxylic acids such as pyridine-2-carboxylic acid, and benzofuran-2-carboxylic acid did not furnish any desired product. It was found that *o*,*o*-dialkoxy substitution is essential for decarboxylative coupling at room temperature presumably due to coordination between oxygen and arylpalladium species.

Next we turned our attention to the pentafluoroarenes as they exhibit distinct chemical and physical properties to their hydrocarbon counterpart.[9] Also an increasing use of perfluorinated compounds in material science, biomedical and bioanalytical research, defense, refrigeration, and domestic appliances has been observed.[10] Therefore, introduction of perfluorinated moiety into the organic backbone has become a fascinating field of research in the last years.[11] However, the metal-catalyzed cross-coupling reaction with this highly electron-deficient arenes poses a great challenge, due to poor coordination with the metal center and reluctance to undergo cross-coupling. A seminal work of palladium-catalyzed Heck coupling between pentafluorohalobenzene (X = I, Br) and styrenes was reported by the Espinet and Milstein groups.[12] Recently, an oxidative Heck coupling between pentafluorobenzene and styrenes were reported by the Zhang group,[13a] and a decarboxylative allylation of pentafluorobenzoates was reported by the Goo$\beta$en group at 120 and 110 °C

**Scheme 2. Substrate Scope with Electron-Rich Carboxylic Acids**[a,b,c]




[a]Conditions: The reaction was carried out in 0.2 mmol scale, 0.06 M. [b]Yield referred to here is the average of at least two experiments. [c]Unless otherwise stated *E*/*Z* ratio of the Heck products are >20:1 as determined by $^1$H NMR. [d]20 mol % $Pd(TFA)_2$ and 3.0 equiv BQ were used. [e]Reaction time 48 h.

respectively.[13b] Direct oxidative cross-coupling with perfluoroarenes also an emerging field of research.[14]

To examine decarboxylative Heck coupling with electron-deficient substrates, pentafluorobenzoic acid was employed under the optimized reaction conditions but no product was formed. Since $Pd^{II}/Ag^{I}$ combination is essential for the



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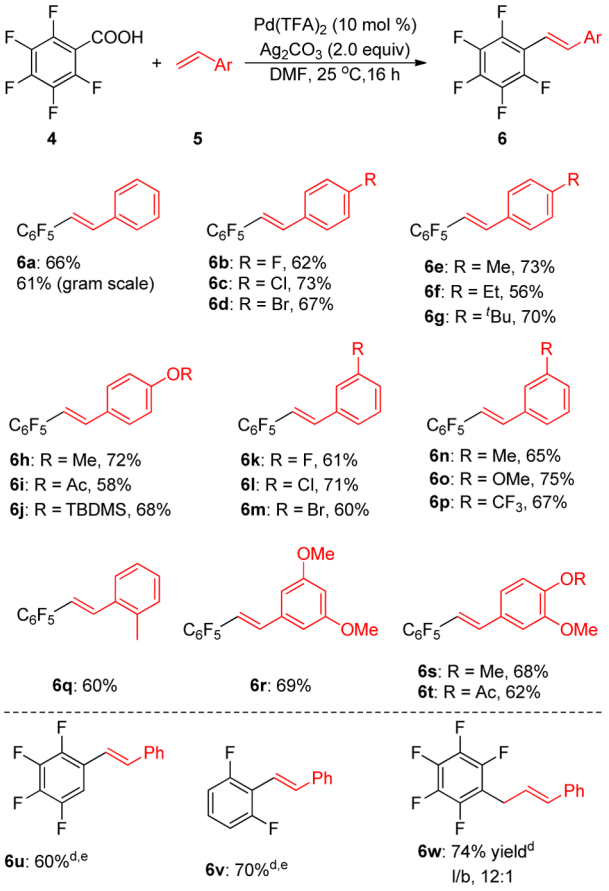
decarboxylative coupling of electron-deficient substrates,[15] benzoquinone was replaced by silver carbonate. Still no Heck product was isolated. Surprisingly, the reaction in pure DMF provided the Heck product at room temperature. This is in sharp contrast to the earlier reports where addition of 5% dimethyl sulfoxide (DMSO) in dimethylformamide (DMF) was found to improve the yield at elevated temperature. Finally, the desired Heck-products were obtained with 10 mol % $Pd(tfa)_2$ and 2.0 equiv of $Ag_2CO_3$ in good yields after 16 h stirring at room temperature.

With this optimized reaction conditions we explored the substrate scope. A wide variety of substituted styrenes provided the Heck product in high yields. Besides alkyl substituents, halogens (**6b**−**6d**, **6k**−**6m**, Scheme 3), labile acetoxy (**6i**, **6t**, Scheme 3) and *tert*-butyldimethylsilyloxy (**6j**, Scheme 3) groups were compatible under these mild reaction conditions. The reaction was also reproduced in gram scale in comparable yield. However, 2,3,4,5-tetrafluoro and 2,6-difluoro benzoic acids provided the coupling product at 120 °C (**6u**, **6v**, Scheme 3). Interestingly, the reaction with allylbenzene at 120 °C provided the corresponding allylation product in high yield and selectivity (**6w**, Scheme 3). Activated alkenes such as methyl acrylate afforded only a trace amount of Heck product under the same reaction conditions.

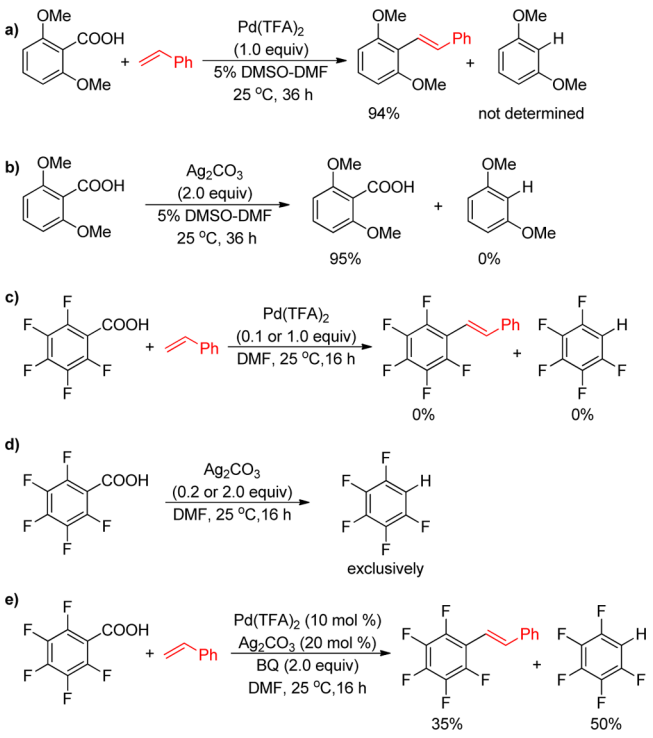
**Scheme 3. Substrate Scope with Perfluorobenzoic Acids**[a,b,c]




[a]Conditions: The reaction was carried out in 0.2 mmol scale, 0.06 M. [b]Yield referred to here is the average of at least two experiments. [c]*E*/*Z* ratio of the Heck products are >20:1 as determined by $^1$H NMR. [d]120 °C was used. [e]20 mol % $Pd(TFA)_2$, 3.0 equiv $Ag_2CO_3$ and 5% DMSO−DMF were used, reaction time 4 h.

**Reaction Mechanism.** In their report, the Myers group applied a general reaction conditions for electron-rich and electron-deficient carboxylic acids. In addition, experimental and theoretical mechanistic investigation was performed exclusively based on the electron-rich substrates.[16] In their study with catalytic and stoichiometric palladium(II)-trifluoroacetate, it was observed that decarboxylation occurs by palladium salt where silver salt acts as an oxidant for catalytic turnover.[16b] However, the mechanism for electron-deficient substrate was illusive. In this present study, we have also observed that electron-rich 2,6-dimethoxybenzoic acid undergoes decarboxylative Heck reaction by a catalytic amount of palladium(II) trifluoroacetate where silver(I) carbonate was replaced by benzoquinone for practical applications. A stoichiometric palladium salt also reproduced the same result in the absence of benzoquinone (Scheme 4a). Additionally, a control experiment suggests that even a superstoichiometric amount of silver(I) carbonate (2 equiv) did not furnish decarboxylation of the 2,6-dimethoxybenzoic acid in the absence of palladium at room temperature (Scheme 4b). However, exclusive decarboxylative protonation product was observed by the Larrosa group with 10 mol % Silver(I) carbonate at 120 °C.[17] In sharp contrast, in the absence of silver salt the reaction with electron-deficient pentafluorobenzoic acid did not proceed even with stoichiometric amount of palladium-(II) trifluoroacetate (Scheme 4c). However, either stoichiometric (2 equiv) or a catalytic amount (20 mol %) of silver(I) carbonate resulted in decarboxylative protonation product exclusively (Scheme 4d). Additionally, a catalytic amount of silver(I) carbonate (20 mol %), palladium(II) trifluoroacetate (10 mol %), and benzoquinone (2.0 equiv) afforded the corresponding Heck product from the pentafluorobenzoic acid and styrene albeit in low yield (35%) (Scheme 4e). Therefore, electron-deficient substrates may follow a distinct pathway for

**Scheme 4. Control Experiments**



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the decarboxylative Heck reaction from electron-rich substrates at room temperature. A similar observation was also observed by the Su group where 2,4-dimethoxybenzoic acid underwent decarboxylative protonation with stoichiometric palladium(II)-trifluoroacetate at 80 °C but 2-nitrobenzoic acid was unreactive. On the other hand, electron-deficient 2-nitrobenzoic acid afforded decarboxylative protonation exclusively with super-stoichiometric amount of silver(I) carbonate (3.0 equiv) only. Ultimately, a Pd/Ag bimetallic system was applied for the C-3 selective arylation of indoles with electron-deficient nitro-benzoic acids.[15,18]

Interestingly, in the earlier reports dimethyl sulfoxide (DMSO) or other sulfide ligands exhibited a prominent role in decarboxylative, direct alkenylation or allylic C−H activations where addition of 5% DMSO as a cosolvent was found to improve yields and catalytic efficiency.[2,16,19] From NMR and crystal structure studies, the Myers group has also shown that DMSO acts as a ligand on the arylpalladium species in decarboxylative Heck-type coupling.[16b] In sharp contrast, for the first time we have observed that DMSO or sulfide ligand exhibit a negative role in the decarboxylative alkenylation reaction between pentafluorobenzoic acid and styrene at room temperature. A careful study revealed that the yield of the alkenylation product was decreased successively with the increase of DMSO (Figure 2) with respect to the

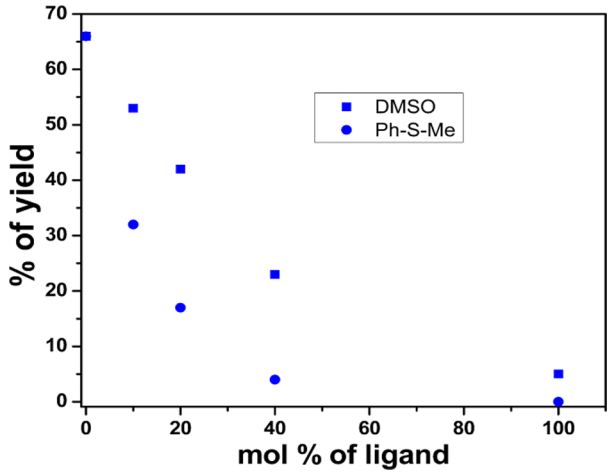
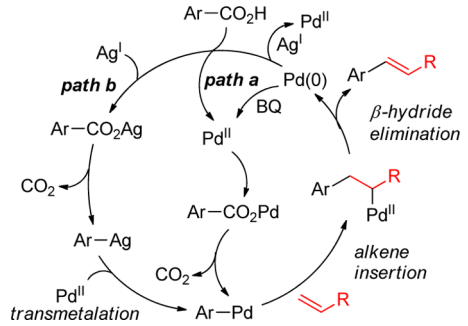



**Figure 2.** Negative role of sulfoxide or sulfide ligand in the heck reaction between pentafluorobenzoic acid and styrene at room temperature.

pentafluorobenzoic acid. In lieu of pure DMF (Scheme 4d), 5% DMSO−DMF also furnished the decarboxylative proto-nation product exclusively suggesting that DMSO has no role in siver-mediated decarboxylation. Therefore, DMSO may act as a ligand on the palladium and influence negatively for the subsequent cross-coupling processes with electron-deficient carboxylic acids. The same trend was also observed with phenyl methyl sulfide. Although, the exact reason for this negative effect of DMSO is not clear at this moment but this room temperature decarboxylation will leads to the development of new cross-coupling reactions under mild conditions.

On the basis of earlier reports and the present study it is speculated that depending of the electronic nature of the carboxylic acids a mechanistic divergence is observed in the decarboxylative Heck coupling reaction. The electron-rich substrates may follow a palladium-catalyzed decarboxylation where dimethyl sulfoxide acts as a ligand and benzoquinone plays as an oxidant for catalytic turnover as shown in *path a*, Scheme 5.[1h] Whereas, pentafluorobenzoic acid may undergo a

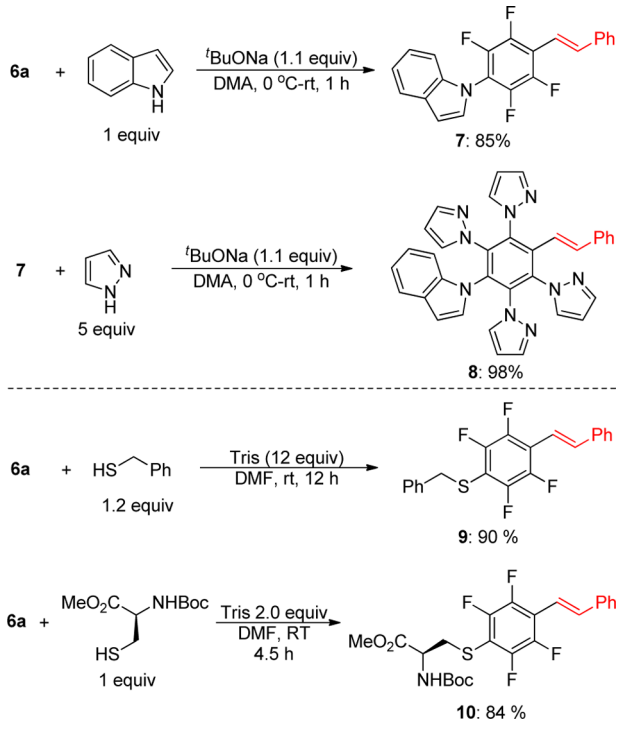
**Scheme 5. Plausible Mechanism**




silver-assisted decarboxylation which forms a arylpalladium species after transmetalation as depicted in *path b*, Scheme 5. Subsequently, the arylpalladium species undergoes migratory alkene insertion and *β*-hydride elimination to provide the Heck product and palladium(0). Finally, the palladium(0) is oxidized either by silver(I) salt or benzoquinone in *path a* and *path b* respectively to complete the catalytic cycle.

Next we turned our attention to utilize the decarboxylative Heck product for further useful transformations. Under basic conditions, the pentafluoroarene moiety, **6a** undergoes an activated aromatic nucleophilic substitution ($S_NAr$) with indole selectively at the *para*-position to afford (**7**, Scheme 6). The remaining fluorenes are further substituted by excess pyrazoles to provide (**8**, Scheme 6).[20] Development of novel synthetic methods for the postsynthetic modification of peptide is an attractive research field.[21] In this vein, we have applied the decarboxylative Heck product for the arylation with cysteine.

**Scheme 6. Product Derivatization**



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To demonstrate with the sulfur nucleophiles, the Heck product **6a** was reacted with benzyl mercaptan to afford (**9**, Scheme 6) in excellent yield. Similarly, it also underwent activated aromatic nucleophilic substitution ($S_NAr$) with the protected cysteine selectively at the *para*-position to provide (**10**, Scheme 6).

## CONCLUSION

In conclusion, we have developed a decarboxylative Heck-type coupling between arene carboxylic acids and alkenes at room temperature. A substrate-dependent mechanistic divergence was observed where electron-rich arene carboxylic acids undergo palladium-catalyzed decarboxylation and electron-deficient arene carboxylic acids undergo silver-assisted decarboxylation. Similarly, dimethyl sulfoxide or other sulfide ligands exhibit positive and negative roles respectively in the present transformation. The pentafluoroarene moiety obtained from the cross-coupling was further derivatized via activated aromatic nucleophilic substitution ($S_NAr$) with nitrogen and sulfur nucleophiles. Therefore, this room temperature reaction sequence is useful for peptide modification under mild reaction conditions.

## EXPERIMENTAL SECTION

**General Information.** Melting points were determined in open end-capillary tubes and are uncorrected. TLC was performed on silica gel plates (Merck silica gel 60, f254), and the spots were visualized with UV light (254 and 365 nm) and $KMnO_4$ stain. $^1H$ and $^{13}C\{^1H\}$ NMR spectra were recorded in $CDCl_3$ using TMS as the internal standard. The $^{19}F$ NMR spectra were recorded in $CDCl_3$ solvent using hexafluorobenzene as the internal standard. HRMS ($m/z$) were measured using EI (magnetic sector, positive ion) and ESI (Q-TOF, positive ion) techniques. Infrared (IR) spectra were recorded on Fourier transform infrared spectroscopy; only intense peaks were reported.

**General Experimental Procedure for the Decarboxylative Heck Reaction between Electron-Rich Carboxylic Acids and Alkenes.** To an oven-dried 15 mL sealed tube, a mixture of carboxylic acids (0.20 mmol, 1.0 equiv), palladium(II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv) and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv) was taken. Then dry DMF (3.0 mL) and DMSO (0.15 mL) were added to it. After purging the reaction vessel with nitrogen, the corresponding alkene (0.30 mmol, 1.5 equiv) was added to the reaction mixture via microliter syringe and the vessel was sealed with a screw cap. The reaction mixture was allowed to stir for 36 h at room temperature. After completion (as detected by TLC), the reaction mixture was poured into water (20 mL) and extracted with ethyl acetate (30 mL). The organic layer was washed with aqueous NaOH solution (2 N, 10 mL), water (10 mL), and brine solution (10 mL), dried over anhydrous $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography using ethyl acetate/hexane as eluent to afford the desired product.

*1-(2,6-Dimethoxystyryl)benzene,* ***3a****, Scheme 2.*[22] The same general procedure was followed by using 2,6-dimethoxybenzoic acid (36.5 mg, 0.2 mmol, 1.0 equiv), styrene (35 μL, 0.3 mmol, 1.5 equiv), palladium(II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 96:4 hexane/ethyl acetate) afforded the desired product as a colorless oil, (45 mg, 94%). $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.61 (d, $J$ = 6.8 Hz, 1H), 7.57 (d, $J$ = 7.8 Hz, 2H), 7.49 (d, $J$ = 16.5 Hz, 1H), 7.37 (t, $J$ = 7.2 Hz, 2H), 7.24 (t, $J$ = 7.5 Hz, 1H), 7.19 (t, $J$ = 8.4 Hz, 1H), 6.62 (d, $J$ = 8.4 Hz, 2H), 3.92 (s, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) $\delta$ 158.5, 139.2, 132.2, 128.4, 128.0, 126.8, 126.3, 119.8, 114.6, 103.9, 55.7; IR (neat) $\upsilon_{max}$ 2934, 1584, 1470, 1248, 1106, 976, 749 $cm^{-1}$; HRMS (EI, $m/z$) calcd. for $C_{16}H_{16}O_2$ $[M]^+$ 240.1150, found 240.1157.

*1-(2,6-Dimethoxystyryl)-4-tert-butylbenzene,* ***3b****, Scheme 2.* The same general procedure was followed by using 2,6-dimethoxybenzoic acid (36.5 mg, 0.2 mmol, 1.0 equiv), 4-*tert*-butylstyrene (55 μL, 0.3 mmol, 1.5 equiv), palladium(II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 96:4 hexane/ethyl acetate) afforded the desired product as a white solid, (56 mg, 94%), mp 98−100 °C. $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.54 (d, $J$ = 16.8 Hz, 1H), 7.42−7.48 (m, 3H), 7.35 (d, $J$ = 8.4 Hz, 2H), 7.14 (t, $J$ = 8.4 Hz, 1H), 6.58 (d, $J$ = 8.1 Hz, 2H), 3.87 (s, 6H), 1.33 (s, 9H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) $\delta$ 158.6, 149.9, 136.6, 132.2, 127.8, 126.1, 125.4, 119.2, 115.1, 104.0, 55.8, 34.5, 31.3; IR (neat) $\upsilon_{max}$ 2958, 1581, 1470, 1252, 1108, 770 $cm^{-1}$; HRMS (ESI, $m/z$) calcd. for $C_{20}H_{24}O_2Na$ $[M + Na]^+$ 319.1674, found 319.1694.

*1-(2,6-Dimethoxystyryl)-4-fluorobenzene,* ***3c****, Scheme 2.* The same general procedure was followed by using 2,6-dimethoxybenzoic acid (36.5 mg, 0.2 mmol, 1.0 equiv), 4-fluorostyrene (36 μL, 0.3 mmol, 1.5 equiv), palladium(II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 96:4 hexane/ethyl acetate) afforded the desired product as a colorless oil, (45 mg, 87%). $^1H$ NMR (600 MHz, $CDCl_3$) $\delta$ 7.57 (d, $J$ = 16.8 Hz, 1H), 7.51−7.54 (m, 2H), 7.40 (d, $J$ = 16.8 Hz, 1H), 7.20 (t, $J$ = 8.4 Hz, 1H), 7.05 (t, $J$ = 8.4 Hz, 2H), 6.62 (d, $J$ = 8.4 Hz, 2H), 3.92 (s, 6H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) $\delta$ 162.0 (d, $J$ = 244.5 Hz), 158.6, 135.4 (d, $J$ = 3.0 Hz), 131.1, 128.1, 127.8 (d, $J$ = 7.5 Hz), 119.6 (d, $J$ = 1.5 Hz), 115.3 (d, $J$ = 2.1 Hz), 114.6, 104.0, 55.8; $^{19}F$ NMR (470 MHz, $CDCl_3$) $\delta$ −119.0 (s, 1F); IR (neat) $\upsilon_{max}$ 2935, 1590, 1506, 1470, 1246, 1106, 775 $cm^{-1}$; HRMS (ESI, $m/z$) calcd. for $C_{16}H_{15}FO_2Na$ $[M + Na]^+$ 281.0954, found 281.0929.

*1-(2,6-Dimethoxystyryl)-4-chlorobenzene,* ***3d****, Scheme 2.* The same general procedure was followed by using 2,6-dimethoxybenzoic acid (36.5 mg, 0.2 mmol, 1.0 equiv), 4-chlorostyrene (38 μL, 0.3 mmol, 1.5 equiv), palladium(II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 96:4 hexane/ethyl acetate) afforded the desired product as a colorless oil, (45 mg, 82%). $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.54 (d, $J$ = 16.8 Hz, 1H), 7.41−7.48 (m, 3H), 7.30 (d, $J$ = 8.4 Hz, 2H), 7.18 (t, $J$ = 8.1 Hz, 1H), 6.60 (d, $J$ = 8.4 Hz, 2H), 3.90 (s, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) $\delta$ 158.6, 137.8, 132.4, 130.9, 128.6, 128.4, 127.6, 120.5, 114.4, 103.9, 55.8; IR (neat) $\upsilon_{max}$ 2935, 1585, 1484, 1249, 1109, 975, 774 $cm^{-1}$; HRMS (ESI, $m/z$) calcd. for $C_{16}H_{15}ClO_2Na$ $[M + Na]^+$ 297.0658, found 297.0681.

*1-(2,6-Dimethoxystyryl)-4-bromobenzene,* ***3e****, Scheme 2.* The same general procedure was followed by using 2,6-dimethoxybenzoic acid (36.5 mg, 0.2 mmol, 1.0 equiv), 4-bromostyrene (40 μL, 0.3 mmol, 1.5 equiv), palladium(II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 96:4 hexane/ethyl acetate) afforded the desired product as a colorless oil, (47 mg, 74%). $^1H$ NMR (600 MHz, $CDCl_3$) $\delta$ 7.53 (d, $J$ = 16.8 Hz, 1H), 7.46−7.48 (m, 3H), 7.42 (d, $J$ = 8.4 Hz, 2H), 7.20 (t, $J$ = 8.4 Hz, 1H), 6.61 (d, $J$ = 8.4 Hz, 2H), 3.91 (s, 6H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) $\delta$ 158.6, 138.3, 131.5, 130.9, 128.4, 127.9, 120.6, 120.5, 114.4, 103.9, 55.8; IR (neat) $\upsilon_{max}$ 2935, 1584, 1475, 1249, 1106, 772 $cm^{-1}$; HRMS (ESI, $m/z$) calcd. for $C_{16}H_{15}BrO_2Na$ $[M + Na]^+$ 341.0153, found 341.0155.

*2-(4-Methoxystyryl)-1,3-dimethoxybenzene,* ***3f****, Scheme 2.*[23] The same general procedure was followed by using 2,6-dimethoxybenzoic acid (36.5 mg, 0.2 mmol, 1.0 equiv), 4-vinylanisole (40 μL, 0.3 mmol, 1.5 equiv), palladium(II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 95:5 hexane/ethyl acetate) afforded the desired product as a white solid, (32 mg, 60%), mp 71−73 °C. $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.54 (d, $J$ = 16.5 Hz, 1H), 7.49 (d, $J$ = 8.7 Hz, 2H), 7.33 (d, $J$ = 16.5 Hz, 1H), 7.16 (t, $J$ = 8.4 Hz, 1H), 6.90 (d, $J$ = 8.7 Hz, 2H), 6.60 (d, $J$ = 8.4 Hz, 2H), 3.90 (s, 6H), 3.84 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) $\delta$ 158.8, 158.4, 132.0, 131.8, 127.6, 127.5, 117.8, 114.9, 113.8, 103.9, 55.7, 55.2; IR (neat)



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$\upsilon_{max}$ 2937, 1601, 1581, 1469, 1249, 1106, 1033, 773 $cm^{-1}$; HRMS (EI, *m*/*z*) calcd. for $C_{17}H_{18}O_3$ $[M]^+$ 270.1256, found 270.1257.

*4-(2,6-Dimethoxystyryl)phenyl acetate,* ***3g****, Scheme 2.* The same general procedure was followed by using 2,6-dimethoxybenzoic acid (36.5 mg, 0.2 mmol, 1.0 equiv), 4-acetoxystyrene (46 μL, 0.3 mmol, 1.5 equiv), palladium(II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 95:5 hexane/ethyl acetate) afforded the desired product as a colorless oil, (57 mg, 95%). $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.54−7.60 (m, 3H), 7.42 (d, *J* = 16.5 Hz, 1H), 7.19 (t, *J* = 8.4 Hz, 1H), 7.08 (d, *J* = 8.4 Hz, 2H), 6.61 (d, *J* = 8.4 Hz, 2H), 3.91 (s, 6H), 2.32 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 171.3, 160.1, 151.3, 138.9, 133.0, 129.9, 129.0, 123.3, 122.0, 116.3, 105.7, 57.5, 22.9; IR (neat) $\upsilon_{max}$ 2937, 1760, 1584, 1504, 1195, 1105, 772 $cm^{-1}$; HRMS (ESI, *m*/*z*) calcd. for $C_{18}H_{18}O_4Na$ $[M + Na]^+$ 321.1103, found 321.1115.

*1-(2,6-Dimethoxystyryl)-3-nitrobenzene,* ***3h****, Scheme 2.* The same general procedure was followed by using 2,6-dimethoxybenzoic acid (36.5 mg, 0.2 mmol, 1.0 equiv), 3-nitrostyrene (42 μL, 0.3 mmol, 1.5 equiv), palladium(II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 95:5 hexane/ethyl acetate) afforded the desired product as a yellow solid, (53 mg, 93%), mp 116−118 °C. $^1H$ NMR (600 MHz, $CDCl_3$) δ 8.37 (s, 1H), 8.04−8.06 (m, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.59−7.66 (m, 2H), 7.49 (t, *J* = 8.4 Hz, 1H), 7.23 (t, *J* = 8.4 Hz, 1H), 6.62 (d, *J* = 8.4 Hz, 2H), 3.93 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 158.8, 148.6, 141.2, 132.0, 129.6, 129.2, 129.1, 122.9, 121.3, 120.9, 113.7, 103.9, 55.8; IR (neat) $\upsilon_{max}$ 1527, 1473, 1343, 1107, 737 $cm^{-1}$; HRMS (EI, *m*/*z*) calcd. for $C_{16}H_{15}NO_4$ $[M]^+$ 285.1001, found 285.1013.

*(E)-1-(2,6-Dimethoxyphenyl)-2-(3,5-dimethoxyphenyl)ethene,* ***3i****, Scheme 2.* The same general procedure was followed by using 2,6-dimethoxybenzoic acid (36.5 mg, 0.2 mmol, 1.0 equiv), 3,5-dimethoxystyrene (49 mg, 0.3 mmol, 1.5 equiv), palladium(II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (50 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a colorless oil, (45 mg, 84%). $^1H$ NMR (600 MHz, $CDCl_3$) δ 7.53 (d, *J* = 16.8 Hz, 1H), 7.46 (d, *J* = 16.8 Hz, 1H), 7.19 (t, *J* = 8.4 Hz, 1H), 6.73 (d, *J* = 1.8 Hz, 2H), 6.61 (d, *J* = 8.4 Hz, 2H), 6.40 (t, *J* = 2.4 Hz, 1H), 3.91 (s, 6H), 3.86 (s, 6H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 160.8, 158.6, 141.4, 132.3, 128.2, 120.4, 114.6, 104.5, 104.0, 99.4, 55.8, 55.3; IR (neat) $\upsilon_{max}$ 2937, 2838, 1587, 1472, 1153, 773 $cm^{-1}$; HRMS (ESI, *m*/*z*) calcd. for $C_{18}H_{20}O_4Na$ $[M + Na]^+$ 323.1259, found 323.1278.

*2-(2,6-Dimethoxystyryl)naphthalene,* ***3j****, Scheme 2.* The same general procedure was followed by using 2,6-dimethoxybenzoic acid (36.5 mg, 0.2 mmol, 1.0 equiv), 2-vinylnaphthalene (46 mg, 0.3 mmol, 1.5 equiv), palladium(II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 96:4 hexane/ethyl acetate) afforded the desired product as a white solid, (50 mg, 86%), mp 136−138 °C. $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.75−7.87 (m, 6H), 7.62 (d, *J* = 16.8 Hz, 1H), 7.40−7.49 (m, 2H), 7.20 (t, *J* = 8.4 Hz, 1H), 6.63 (d, *J* = 8.4 Hz, 2H), 3.94 (s, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 158.7, 136.9, 133.9, 132.9, 132.4, 128.2, 128.0, 127.96, 127.7, 126.2, 126.1, 125.4, 123.8, 120.4, 114.9, 104.1, 55.8; IR (neat) $\upsilon_{max}$ 1583, 1470, 1242, 1105, 772 $cm^{-1}$; HRMS (EI, *m*/*z*) calcd. for $C_{20}H_{18}O_2$ $[M]^+$ 290.1307, found 290.1310.

*1-(2,6-Dimethoxystyryl)-2,3,4,5,6-pentafluorobenzene,* ***3k****, Scheme 2.* The same general procedure was followed by using 2,6-dimethoxybenzoic acid (36.5 mg, 0.2 mmol, 1.0 equiv), pentafluorostyrene (42 μL, 0.3 mmol, 1.5 equiv), palladium(II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 96:4 hexane/ethyl acetate) afforded the desired product as a white solid, (56 mg, 85%), mp 146−148 °C. $^1H$ NMR (600 MHz, $CDCl_3$) δ 7.75 (d, *J* = 17.4 Hz, 1H), 7.47 (d, *J* = 16.8 Hz, 1H), 7.24 (t, *J* = 8.4 Hz, 1H), 6.61 (d, *J* = 8.4 Hz, 2H), 3.92 (s, 6H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 158.9, 144.6 (dm, *J* = 249.0 Hz), 139.1, (dm, *J* = 250.5 Hz), 137.7 (dm, *J* = 247.5 Hz), 129.6, 128.6 (t, *J* = 9.0 Hz), 116.2, 114.2 (td, *J* = 13.5 Hz, 4.5 Hz), 113.8, 103.8, 55.8 (d, *J* = 3.0 Hz); $^{19}F$ NMR (470 MHz, $CDCl_3$) δ −144.6 (dd, *J* = 26.8 Hz, 8.9 Hz, 2F), −159.5 (t, *J* = 26.3 Hz, 1F), −165.0 (td, *J* = 26.3 Hz, 8.9 Hz, 2F); IR (neat) $\upsilon_{max}$ 1585, 1496, 1245, 1108, 1000, 774 $cm^{-1}$; HRMS (EI, *m*/*z*) calcd. for $C_{16}H_{11}F_5O_2$ $[M]^+$ 330.0679, found 330.0665.

*2-(2-Methoxystyryl)-1,3-dimethoxybenzene,* ***3l****, Scheme 2.* The same general procedure was followed by using 2,6-dimethoxybenzoic acid (36.5 mg, 0.2 mmol, 1.0 equiv), 2-vinylanisole (40 μL, 0.3 mmol, 1.5 equiv), palladium(II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 96:4 hexane/ethyl acetate) afforded the desired product as a white solid, (41 mg, 76%), mp 66−68 °C. $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.87 (d, *J* = 16.8 Hz, 1H), 7.64 (dd, *J* = 7.5 Hz, 0.9 Hz, 1H), 7.39 (d, *J* = 16.8 Hz, 1H), 7.11−7.25 (m, 2H), 6.96 (t, *J* = 7.5 Hz, 1H), 6.87 (d, *J* = 8.1 Hz, 1H), 6.58 (d, *J* = 8.4 Hz, 2H), 3.88 (s, 6H), 3.86 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 158.6, 156.7, 128.6, 128.0, 127.8, 127.2, 126.2, 120.7, 120.4, 115.4, 110.8, 104.0, 55.8, 55.6; IR (neat) $\upsilon_{max}$ 2935, 2837, 1586, 1468, 1243, 1106, 746 $cm^{-1}$; HRMS (ESI, *m*/*z*) calcd. for $C_{17}H_{18}O_3Na$ $[M + Na]^+$ 293.1154, found 293.1147.

*1,4-Bis(2,6-dimethoxystyryl)benzene,* ***3m****, Scheme 2.* The same general procedure was followed by using 2,6-dimethoxybenzoic acid (36.5 mg, 0.2 mmol, 1.0 equiv), 1,4-divinylbenzene (22 μL, 0.15 mmol, 0.75 equiv), palladium(II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a yellow solid, (29 mg, 72%), mp 180−182 °C. $^1H$ NMR (600 MHz, $CDCl_3$) δ 7.61 (d, *J* = 16.2 Hz, 2H), 7.54 (s, 4H), 7.50 (d, *J* = 16.8 Hz, 2H), 7.18 (t, *J* = 8.4 Hz, 2H), 6.62 (d, *J* = 8.4 Hz, 4H), 3.93 (s, 12H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 158.6, 138.0, 132.2, 127.9, 126.5, 119.3, 115.0, 104.0, 55.8; IR (neat) $\upsilon_{max}$ 1582, 1472, 1251, 1105, 770 $cm^{-1}$; HRMS (EI, *m*/*z*) calcd. for $C_{26}H_{26}O_4$ $[M]^+$ 402.1831, found 402.1833.

*(E)-3-(2,6-Dimethoxyphenyl)acrylonitrile,* ***3n****, Scheme 2.* The same general procedure was followed by using 2,6-dimethoxybenzoic acid (36.5 mg, 0.2 mmol, 1.0 equiv), acrylonitrile (20 μL, 0.3 mmol, 1.5 equiv), palladium(II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a colorless oil, (24 mg, 64%). $^1H$ NMR (600 MHz, $CDCl_3$) δ 7.82 (d, *J* = 16.8 Hz, 1H), 7.28−7.34 (m, 2H), 7.22 (d, *J* = 12.0 Hz, 1H), 6.59 (d, *J* = 8.4 Hz, 2H), 6.57 (d, *J* = 8.4 Hz, 2H), 6.42 (d, *J* = 16.8 Hz, 1H), 5.58 (d, *J* = 12.0 Hz, 1H), 3.89 (s, 12H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 158.8, 158.2, 141.4, 141.0, 132.0, 131.6, 120.2, 117.3, 111.9, 111.6, 103.7, 103.6, 99.9, 98.4, 55.8, 55.4; IR (neat) $\upsilon_{max}$ 2936, 2210, 1696, 1601, 1475, 1249, 1112, 777 $cm^{-1}$; HRMS (ESI, *m*/*z*) calcd. for $C_{11}H_{11}NO_2Na$ $[M + Na]^+$ 212.0687, found 212.0691.

*(E)-Methyl 3-(2,6-dimethoxyphenyl)acrylate,* ***3o****, Scheme 2.*[1h] The same general procedure was followed by using 2,6-dimethoxybenzoic acid (36.5 mg, 0.2 mmol, 1.0 equiv), methyl acrylate (27 μL, 0.3 mmol, 1.5 equiv), palladium(II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a white solid, (36 mg, 81%), mp 70−72 °C. $^1H$ NMR (300 MHz, $CDCl_3$) δ 8.14 (d, *J* = 16.2 Hz, 1H), 7.26 (t, *J* = 8.4 Hz, 1H), 6.88 (d, *J* = 16.2 Hz, 1H), 6.55 (d, *J* = 8.4 Hz, 2H), 3.87 (s, 6H), 3.79 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 169.0, 160.0, 135.6, 131.2, 120.2, 112.1, 103.6, 55.7, 51.4; IR (neat) $\upsilon_{max}$ 2942, 1703, 1618, 1255, 1161, 1104, 748 $cm^{-1}$; HRMS (EI, *m*/*z*) calcd. for $C_{12}H_{14}O_4$ $[M]^+$ 222.0892, found 222.0902.

*(E)-Butyl 3-(2,6-dimethoxyphenyl)acrylate,* ***3p****, Scheme 2.* The same general procedure was followed by using 2,6-dimethoxybenzoic acid (36.5 mg, 0.2 mmol, 1.0 equiv), butyl acrylate (43 μL, 0.3 mmol, 1.5 equiv), palladium(II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a colorless oil, (39 mg, 74%). $^1H$ NMR (300 MHz, $CDCl_3$) δ 8.14 (d, *J* = 16.2 Hz, 1H), 7.26 (t, *J* = 8.4 Hz, 1H),


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6.88 (d, $J$ = 16.5 Hz, 1H), 6.55 (d, $J$ = 8.4 Hz, 2H), 4.20 (t, $J$ = 6.6 Hz, 2H), 3.88 (s, 6H), 1.64−1.74 (m, 2H), 1.38−1.50 (m, 2H), 0.96 (t, $J$ = 7.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) $\delta$ 168.6, 159.8, 135.2, 131.0, 120.5, 112.1, 103.5, 63.9, 55.6, 30.8, 19.1, 13.7; IR (neat) $\upsilon_{max}$ 2959, 1706, 1623, 1587, 1474, 1255, 1109, 744 $cm^{-1}$; HRMS (EI, $m/z$) calcd. for $C_{15}H_{20}O_4$ $[M]^+$ 264.1362, found 264.1346.

*(E)-Phenyl 3-(2,6-dimethoxyphenyl)acrylate,* ***3q****, Scheme 2.* The same general procedure was followed by using 2,6-dimethoxybenzoic acid (36.5 mg, 0.2 mmol, 1.0 equiv), phenyl acrylate (45 mg, 0.3 mmol, 1.5 equiv), palladium(II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a white solid, (41.5 mg, 73%), mp 106−108 °C. $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 8.36 (d, $J$ = 16.2 Hz, 1H), 7.42 (t, $J$ = 7.8 Hz, 2H), 7.33 (t, $J$ = 8.4 Hz, 1H), 7.26 (d, $J$ = 8.1 Hz, 1H), 7.20 (d, $J$ = 7.5 Hz, 2H), 7.11 (d, $J$ = 16.2 Hz, 1H), 6.61 (d, $J$ = 8.4 Hz, 2H), 3.93 (s, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) $\delta$ 167.0, 160.2, 151.2, 137.4, 131.8, 129.4, 125.5, 121.9, 119.6, 112.1, 103.7, 55.8; IR (neat) $\upsilon_{max}$ 1735, 1619, 1478, 1254, 1131, 738 $cm^{-1}$; HRMS (ESI, $m/z$) calcd. for $C_{17}H_{16}O_4Na$ $[M + Na]^+$ 307.0946, found 307.0957.

*(E)-Methyl 3-(2,6-dimethoxyphenyl)-2-methyl acrylate,* ***3r****, Scheme 2.*[24] The same general procedure was followed by using 2,6-dimethoxybenzoic acid (36.5 mg, 0.2 mmol, 1.0 equiv), methyl methacrylate (32 $\mu$L, 0.3 mmol, 1.5 equiv), palladium(II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a colorless oil, (19 mg, 40%). $^1H$ NMR (600 MHz, $CDCl_3$) $\delta$ 7.54 (s, 1H), 7.28 (t, $J$ = 8.4 Hz, 1H), 6.59 (d, $J$ = 8.4 Hz, 2H), 3.83 (s, 6H), 3.81 (s, 3H), 1.79 (d, $J$ = 1.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) $\delta$ 168.7, 157.7, 131.9, 130.9, 129.7, 113.4, 103.5, 55.6, 51.8, 15.2; IR (neat) $\upsilon_{max}$ 2950, 2840, 1710, 1587, 1470, 1253, 1105, 745 $cm^{-1}$; HRMS (ESI, $m/z$) calcd. for $C_{13}H_{16}O_4Na$ $[M + Na]^+$ 259.0946, found 259.0934.

*1-((E)-3-(2,6-Dimethoxyphenyl)prop-1-enyl)benzene,* ***3s****, Scheme 2.* The same general procedure was followed by using 2,6-dimethoxybenzoic acid (36.5 mg, 0.2 mmol, 1.0 equiv), allylbenzene (40 $\mu$L, 0.3 mmol, 1.5 equiv), palladium(II) trifluoroacetate (13.4 mg, 0.04 mmol, 0.1 equiv), and 1,4-benzoquinone (65 mg, 0.4 mmol, 3.0 equiv). Column chromatography ($SiO_2$, eluting with 95:5 hexane/ethyl acetate) afforded the desired product as a colorless oil, (28 mg, 55%). $^1H$ NMR (600 MHz, $CDCl_3$) $\delta$ 7.33 (d, $J$ = 7.2 Hz, 2H), 7.25−7.28 (m, 2H), 7.13−7.20 (m, 2H), 7.09 (d, $J$ = 8.4 Hz, 2H), 6.32−6.41 (m, 2H), 3.85 (s, 6H), 3.58 (d, $J$ = 6.0 Hz, 2H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) $\delta$ 158.2, 138.1, 129.4, 129.0, 128.3, 127.1, 126.5, 126.0, 116.5, 103.8, 55.8, 26.4; IR (neat) $\upsilon_{max}$ 2927, 1728, 1593, 1469, 1254, 1110, 729 $cm^{-1}$; HRMS (ESI, $m/z$) calcd. for $C_{17}H_{18}O_2Na$ $[M + Na]^+$ 277.1204, found 277.1179.

*1-Fluoro-4-((E)-3-(2,6-dimethoxyphenyl)prop-1-enyl)benzene,* ***3t****, Scheme 2.* The same general procedure was followed by using 2,6-dimethoxybenzoic acid (36.5 mg, 0.2 mmol, 1.0 equiv), 4-fluoroallylbenzene (41 $\mu$L, 0.3 mmol, 1.5 equiv), palladium(II) trifluoroacetate (13.4 mg, 0.04 mmol, 0.1 equiv), and 1,4-benzoquinone (65 mg, 0.4 mmol, 3.0 equiv). Column chromatography ($SiO_2$, eluting with 95:5 hexane/ethyl acetate) afforded the desired product as a white solid, (31 mg, 57%), mp 68−70 °C. $^1H$ NMR (600 MHz, $CDCl_3$) $\delta$ 7.28−7.31 (m, 2H), 7.19 (t, $J$ = 8.4 Hz, 1H), 6.96 (t, $J$ = 8.4 Hz, 2H), 6.60 (d, $J$ = 8.4 Hz, 2H), 6.36 (d, $J$ = 15.6 Hz, 1H), 6.25−6.30 (m, 1H), 3.86 (s, 6H), 3.58 (d, $J$ = 6.0 Hz, 2H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) $\delta$ 161.7 (d, $J$ = 243.0 Hz), 158.2, 134.2 (d, $J$ = 3.0 Hz), 128.7 (d, $J$ = 3.0 Hz), 128.3, 127.3 (d, $J$ = 7.5 Hz), 127.2, 116.4, 115.1 (d, $J$ = 21.0 Hz), 103.8, 55.8, 26.4; $^{19}F$ NMR (470 MHz, $CDCl_3$) $\delta$ −119.6 (s, 1F); IR (neat) $\upsilon_{max}$ 2929, 1592, 1470, 1255, 1107, 839 $cm^{-1}$; HRMS (EI, $m/z$) calcd. for $C_{17}H_{17}FO_2$ $[M]^+$ 272.1213, found 272.1208.

*2-(4-Methoxycinnamyl)-1,3-dimethoxybenzene,* ***3u****, Scheme 2.*[8] The same general procedure was followed by using 2,6-dimethoxybenzoic acid (36.5 mg, 0.2 mmol, 1.0 equiv), 4-methoxyallylbenzene (46 $\mu$L, 0.3 mmol, 1.5 equiv), palladium(II) trifluoroacetate (13.4 mg, 0.04 mmol, 0.1 equiv), and 1,4-benzoquinone (65 mg, 0.4 mmol, 3.0 equiv). Column chromatography ($SiO_2$, eluting with 95:5 hexane/ethyl acetate) afforded the desired product as a white solid, (24 mg, 42%), mp 70−72 °C. $^1H$ NMR (600 MHz, $CDCl_3$) $\delta$ 7.26 (d, $J$ = 9.0 Hz, 2H), 7.17 (t, $J$ = 8.4 Hz, 1H), 6.81 (d, $J$ = 8.4 Hz, 2H), 6.58 (d, $J$ = 8.4 Hz, 2H), 6.34 (d, $J$ = 15.6 Hz, 1H), 6.18−6.23 (m, 1H), 3.85 (s, 6H), 3.79 (s, 3H), 3.55 (d, $J$ = 6.6 Hz, 2H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) $\delta$ 158.4, 158.2, 131.1, 128.8, 127.05, 127.02, 126.8, 116.8, 113.7, 103.8, 55.8, 55.2, 26.4; IR (neat) $\upsilon_{max}$ 2930, 1597, 1510, 1469, 1250, 1111, 833 $cm^{-1}$; HRMS (EI, $m/z$) calcd. for $C_{18}H_{20}O_3$ $[M]^+$ 284.1412, found 284.1408.

*2,6-Dimethoxycinnamyl acetate,* ***3v****, Scheme 2.*[8] The same general procedure was followed by using 2,6-dimethoxybenzoic acid (36.5 mg, 0.2 mmol, 1.0 equiv), allylacetate (33 $\mu$L, 0.3 mmol, 1.5 equiv), palladium(II) trifluoroacetate (13.4 mg, 0.04 mmol, 0.1 equiv), and 1,4-benzoquinone (65 mg, 0.6 mmol, 3.0 equiv). Column chromatography ($SiO_2$, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a colorless oil, (32 mg, 67%). $^1H$ NMR (600 MHz, $CDCl_3$) $\delta$ 7.18 (t, $J$ = 8.4 Hz, 1H), 6.99 (d, $J$ = 16.2 Hz, 1H), 6.71−6.76 (m, 1H), 6.56 (d, $J$ = 8.4 Hz, 2H), 4.75 (dd, $J$ = 6.6 Hz, 0.6 Hz, 2H), 3.86 (s, 6H), 2.11 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) $\delta$ 171.0, 158.6, 128.6, 126.8, 125.0, 113.3, 103.8, 67.1, 55.7, 21.1; IR (neat) $\upsilon_{max}$ 2938, 1737, 1587, 1472, 1247, 772 $cm^{-1}$; HRMS (ESI, $m/z$) calcd. for $C_{13}H_{16}O_4Na$ $[M + Na]^+$ 259.0946, found 259.0923.

*3-(2,6-Dimethoxyphenyl)-1-phenylpropan-1-one,* ***3w****, Scheme 2.*[6b] The same general procedure was followed by using 2,6-dimethoxybenzoic acid (36.5 mg, 0.2 mmol, 1.0 equiv), 1-phenylprop-2-en-1-ol (40 $\mu$L, 0.3 mmol, 1.5 equiv), palladium(II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv) except the reaction was run for 48 h. Column chromatography ($SiO_2$, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a white solid, (20.5 mg, 38%), mp 88−90 °C. $^1H$ NMR (600 MHz, $CDCl_3$) $\delta$ 8.02 (dd, $J$ = 8.4 Hz, 1.2 Hz, 2H), 7.54−7.57 (m, 1H), 7.45−7.47 (m, 2H), 7.18 (t, $J$ = 8.4 Hz, 1H), 6.57 (d, $J$ = 8.4 Hz, 2H), 3.81 (s, 6H), 3.14−3.17 (m, 2H), 3.08−3.11 (m, 2H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) $\delta$ 200.6, 158.2, 137.0, 132.7, 128.4, 128.2, 127.1, 117.4, 103.5, 55.6, 38.3, 18.5; IR (neat) $\upsilon_{max}$ 2937, 1682, 1593, 1471, 1254, 1107, 778, 693 $cm^{-1}$; HRMS (ESI, $m/z$) calcd. for $C_{17}H_{18}O_3Na$ $[M + Na]^+$ 293.1154, found 293.1130.

*Diethyl 2-(2,6-dimethoxycinnamyl)malonate,* ***3x****, Scheme 2.*[8] The same general procedure was followed by using 2,6-dimethoxybenzoic acid (36.5 mg, 0.2 mmol, 1.0 equiv), diethyl 2-allylmalonate (60 $\mu$L, 0.3 mmol, 1.5 equiv), palladium(II) trifluoroacetate (13.4 mg, 0.04 mmol, 0.1 equiv), and 1,4-benzoquinone (65 mg, 0.6 mmol, 3.0 equiv). Column chromatography ($SiO_2$, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a colorless oil, (44 mg, 65%). $^1H$ NMR (600 MHz, $CDCl_3$) $\delta$ 7.12 (t, $J$ = 8.4 Hz, 1H), 6.74 (t, $J$ = 16.2 Hz, 1H), 6.51−6.58 (m, 3H), 4.19−4.26 (m, 4H), 3.82 (s, 6H), 3.51 (t, $J$ = 7.8 Hz, 1H), 2.83 (td, $J$ = 7.8 Hz, 1.2 Hz, 2H), 1.28 (t, $J$ = 6.6 Hz, 6H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) $\delta$ 169.1, 158.2, 129.7, 127.7, 123.0, 114.4, 103.9, 61.3, 55.6, 52.5, 34.0, 14.0; IR (neat) $\upsilon_{max}$ 2981, 1732, 1585, 1472, 1251, 1113, 772 $cm^{-1}$; HRMS (ESI, $m/z$) calcd. for $C_{18}H_{24}O_6Na$ $[M + Na]^+$ 359.1471, found 359.1468.

*(E)-4-Methoxybenzyl 5-(2,6-dimethoxyphenyl)pent-4-enoate,* ***3y****, Scheme 2.* The same general procedure was followed by using 2,6-dimethoxybenzoic acid (36.5 mg, 0.2 mmol, 1.0 equiv), 4-methoxybenzyl pent-4-enoate (66 mg, 0.3 mmol, 1.5 equiv), palladium(II) trifluoroacetate (13.4 mg, 0.04 mmol, 0.1 equiv), and 1,4-benzoquinone (65 mg, 0.6 mmol, 3.0 equiv). Column chromatography ($SiO_2$, eluting with 8:2 hexane/ethyl acetate) afforded the desired product as colorless oil, (28.5 mg, 40%). $^1H$ NMR (600 MHz, $CDCl_3$) $\delta$ 7.31 (d, $J$ = 8.4 Hz, 2H), 7.13 (t, $J$ = 8.4 Hz, 1H), 6.88 (d, $J$ = 8.4 Hz, 2H), 6.70 (d, $J$ = 16.2 Hz, 1H), 6.57−6.62 (m, 1H), 6.56 (d, $J$ = 8.4 Hz, 2H), 5.08 (s, 2H), 3.83 (s, 6H), 3.82 (s, 3H), 2.58−2.61 (m, 2H), 2.53−2.56 (m, 2H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) $\delta$ 173.2, 159.5, 158.2, 132.7, 130.0, 128.2, 127.5, 121.2, 114.6, 113.9, 103.9, 65.9, 55.7, 55.2, 34.5, 30.0; IR (neat) $\upsilon_{max}$ 2928, 1732, 1586, 1514, 1469, 1248, 1111, 823 $cm^{-1}$; HRMS (ESI, $m/z$) calcd. for $C_{21}H_{24}O_5Na$ $[M + Na]^+$ 379.1521, found 379.1530.



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*1-(2,6-Diethoxystyryl)benzene,* ***3z****, Scheme 2.* The same general procedure was followed by using 2,6-diethoxybenzoic acid (42 mg, 0.2 mmol, 1.0 equiv), styrene (35 μL, 0.3 mmol, 1.5 equiv), palladium(II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 95:5 hexane/ethyl acetate) afforded the desired product as a white solid, (48 mg, 90%), mp 55−57 °C. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, *J* = 16.5 Hz, 1H), 7.50−7.56 (m, 3H), 7.36 (t, *J* = 7.5 Hz, 2H), 7.21−7.26 (m, 1H), 7.13 (t, *J* = 8.4 Hz, 1H), 6.57 (d, *J* = 8.4 Hz, 2H), 4.12 (q, *J* = 6.9 Hz, 4H), 1.51 (t, *J* = 7.2 Hz, 6H); $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$) δ 158.1, 139.5, 132.1, 128.4, 128.0, 126.8, 126.3, 120.2, 114.8, 104.9, 64.2, 14.9; IR (neat) $\upsilon_{max}$ 2978, 1582, 1458, 1247, 1116, 1083, 748 cm$^{-1}$; HRMS (ESI, *m*/*z*) calcd. for $C_{18}H_{20}O_2Na$ [M + Na]$^+$ 291.1361, found 291.1352.

*1-((3-(Benzyloxy)-2-styrylphenoxy)methyl)benzene,* ***3aa****, Scheme 2.* The same general procedure was followed by using 2,6-dibenzyloxybenzoic acid (67 mg, 0.2 mmol, 1.0 equiv), styrene (35 μL, 0.3 mmol, 1.5 equiv), palladium(II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 95:5 hexane/ethyl acetate) afforded the desired product as a white solid, (59 mg, 75%), mp 88−90 °C. $^1$H NMR (600 MHz, $CDCl_3$) δ 7.70 (d, *J* = 16.8 Hz, 1H), 7.62 (d, *J* = 16.8 Hz, 1H), 7.51 (d, *J* = 7.8 Hz, 4H), 7.41−7.43 (m, 6H), 7.36 (t, *J* = 7.8 Hz, 2H), 7.32 (t, *J* = 7.8 Hz, 2H), 7.21 (t, *J* = 7.2 Hz, 1H), 7.14 (t, *J* = 7.8 Hz, 1H), 6.68 (d, *J* = 8.4 Hz, 2H), 5.19 (s, 4H); $^{13}$C{$^1$H} NMR (150 MHz, $CDCl_3$) δ 157.8, 139.2, 137.1, 132.7, 128.5, 128.4, 127.9, 127.8, 127.2, 126.9, 126.3, 119.7, 115.8, 105.9, 70.8; IR (neat) $\upsilon_{max}$ 2926, 1728, 1582, 1452, 1254, 1104, 741 cm$^{-1}$; HRMS (ESI, *m*/*z*) calcd. for $C_{28}H_{24}O_2Na$ [M + Na]$^+$ 415.1674, found 415.1674.

*1,3,5-Trimethoxy-2-styrylbenzene,* ***3ab****, Scheme 2.*[25] The same general procedure was followed by using 2,4,6-trimethoxybenzoic acid (42.5 mg, 0.2 mmol, 1.0 equiv), styrene (35 μL, 0.3 mmol, 1.5 equiv), palladium(II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a colorless oil, (50 mg, 93%). $^1$H NMR (600 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.8 Hz, 2H), 7.50 (d, *J* = 16.2 Hz, 1H), 7.44 (d, *J* = 16.2 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 2H), 7.22 (t, *J* = 7.2 Hz, 1H), 6.20 (s, 2H), 3.91 (s, 6H), 3.86 (s, 3H); $^{13}$C{$^1$H} NMR (150 MHz, $CDCl_3$) δ 160.2, 159.5, 139.7, 129.9, 128.4, 126.5, 126.1, 119.8, 108.1, 90.8, 55.8, 55.3; IR (neat) $\upsilon_{max}$ 2938, 1597, 1461, 1328, 1210, 1119, 813 cm$^{-1}$; HRMS (ESI, *m*/*z*) calcd. for $C_{17}H_{18}O_3Na$ [M + Na]$^+$ 293.1154, found 293.1140.

*2-(4-Phenylstyryl)-1,3,5-trimethoxybenzene,* ***3ac****, Scheme 2.* The same general procedure was followed by using 2,4,6-trimethoxybenzoic acid (42.5 mg, 0.2 mmol, 1.0 equiv), 4-vinylbiphenyl (54 mg, 0.3 mmol, 1.5 equiv), palladium(II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a white solid, (57 mg, 82%), mp 150−152 °C. $^1$H NMR (600 MHz, $CDCl_3$) δ 7.64−7.66 (m, 2H), 7.59−7.62 (m, 4H), 7.53 (d, *J* = 16.8 Hz, 1H), 7.45−7.49 (m, 3H), 7.35 (t, *J* = 7.2 Hz, 1H), 6.21 (s, 2H), 3.92 (s, 6H), 3.87 (s, 3H); $^{13}$C{$^1$H} NMR (150 MHz, $CDCl_3$) δ 160.3, 159.6, 141.0, 139.1, 138.8, 129.3, 128.7, 127.1, 127.0, 126.8, 126.6, 120.0, 108.2, 90.8, 55.8, 55.3; IR (neat) $\upsilon_{max}$ 1592, 1458, 1326, 1218, 1153, 1119, 766 cm$^{-1}$; HRMS (ESI, *m*/*z*) calcd. for $C_{23}H_{22}O_3Na$ [M + Na]$^+$ 369.1467, found 369.1467.

*2-(2-Methylstyryl)-1,3,5-trimethoxybenzene,* ***3ad****, Scheme 2.*[26] The same general procedure was followed by using 2,4,6-trimethoxybenzoic acid (42.5 mg, 0.2 mmol, 1.0 equiv), 2-methylstyrene (39 μL, 0.3 mmol, 1.5 equiv), palladium(II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a white solid, (51 mg, 90%), mp 86−88 °C. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.62−7.69 (m, 2H), 7.24 (d, *J* = 16.5 Hz, 1H), 7.08−7.19 (m, 3H), 6.17 (s, 2H), 3.87 (s, 6H), 3.84 (s, 3H), 2.39 (s, 3H); $^{13}$C{$^1$H} NMR (150 MHz, $CDCl_3$) δ 160.2, 159.4, 138.7, 135.3, 130.1, 128.0, 126.5, 126.0, 124.9, 120.8, 108.6, 90.8, 55.8, 55.3, 20.0; IR (neat) $\upsilon_{max}$ 2936, 1586, 1460, 1198, 1118, 809 cm$^{-1}$; HRMS (ESI, *m*/*z*) calcd. for $C_{18}H_{20}O_3Na$ [M + Na]$^+$ 307.1310, found 307.1308.

*2-(3-Chlorostyryl)-1,3,5-trimethoxybenzene,* ***3ae****, Scheme 2.*[26] The same general procedure was followed by using 2,4,6-trimethoxybenzoic acid (42.5 mg, 0.2 mmol, 1.0 equiv), 3-chlorostyrene (38 μL, 0.3 mmol, 1.5 equiv), palladium(II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a white solid, (55 mg, 91%), mp 80−82 °C. $^1$H NMR (600 MHz, $CDCl_3$) δ 7.51 (t, *J* = 1.8 Hz, 1H), 7.42 (d, *J* = 1.8 Hz, 2H), 7.38 (d, *J* = 7.8 Hz, 1H), 7.25 (t, *J* = 7.8 Hz, 1H), 7.15−7.17 (m, 1H), 6.19 (s, 2H), 3.90 (s, 6H), 3.86 (s, 3H); $^{13}$C{$^1$H} NMR (150 MHz, $CDCl_3$) δ 160.5, 159.6, 141.7, 134.3, 129.5, 128.2, 126.2, 125.9, 124.3, 121.2, 107.6, 90.7, 55.7, 55.3; IR (neat) $\upsilon_{max}$ 2961, 1586, 1462, 1326, 1220, 1117, 962, 796 cm$^{-1}$; HRMS (ESI, *m*/*z*) calcd. for $C_{17}H_{17}ClO_3Na$ [M + Na]$^+$ 327.0764, found 327.0783.

*4-(2,4,6-Trimethoxystyryl)-2-methoxyphenyl acetate,* ***3af****, Scheme 2.* The same general procedure was followed by using 2,4,6-trimethoxybenzoic acid (42.5 mg, 0.2 mmol, 1.0 equiv), 4-acetoxy-3-methoxystyrene (57 mg, 0.3 mmol, 1.5 equiv), palladium(II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 8:2 hexane/ethyl acetate) afforded the desired product as a white solid, (61 mg, 85%), mp 105−107 °C. $^1$H NMR (600 MHz, $CDCl_3$) δ 7.43 (d, *J* = 16.8 Hz, 1H), 7.33 (d, *J* = 16.2 Hz, 1H), 7.10−7.11 (m, 2H), 7.00 (d, *J* = 8.4 Hz, 1H), 6.19 (s, 2H), 3.898 (s, 3H), 3.896 (s, 6H), 3.86 (s, 3H), 2.33 (s, 3H); $^{13}$C{$^1$H} NMR (150 MHz, $CDCl_3$) δ 169.2, 160.3, 159.5, 150.9, 138.9, 138.4, 129.3, 122.6, 120.2, 118.6, 110.0, 107.9, 90.8, 55.9, 55.8, 55.3, 20.7; IR (neat) $\upsilon_{max}$ 2933, 1761, 1598, 1460, 1118, 817 cm$^{-1}$; HRMS (ESI, *m*/*z*) calcd. for $C_{20}H_{22}O_6Na$ [M + Na]$^+$ 381.1314, found 381.1336.

*(E)-Butyl 3-(2,4,6-trimethoxyphenyl)acrylate,* ***3ag****, Scheme 2.*[27] The same general procedure was followed by using 2,4,6-trimethoxybenzoic acid (42.5 mg, 0.2 mmol, 1.0 equiv), butyl acrylate (43 μL, 0.3 mmol, 1.5 equiv), palladium(II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and 1,4-benzoquinone (43 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 8:2 hexane/ethyl acetate) afforded the desired product as a white solid, (41 mg, 70%), mp 79−81 °C. $^1$H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, *J* = 16.2 Hz, 1H), 6.75 (d, *J* = 16.2 Hz, 1H), 6.11 (s, 2H), 4.19 (t, *J* = 6.6 Hz, 2H), 3.87 (s, 6H), 3.84 (s, 3H), 1.64−1.73 (m, 2H), 1.37−1.50 (m, 2H), 0.96 (t, *J* = 7.5 Hz, 3H); $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$) δ 169.1, 162.6, 161.1, 135.4, 117.4, 105.7, 90.3, 63.8, 55.6, 55.3, 30.9, 19.2, 13.8; IR (neat) $\upsilon_{max}$ 2939, 1699, 1602, 1461, 1156, 1119, 815 cm$^{-1}$; HRMS (ESI, *m*/*z*) calcd. for $C_{16}H_{22}O_5Na$ [M + Na]$^+$ 317.1365, found 317.1360.

*Diethyl 2-(2,4,6-trimethoxycinnamyl)malonate,* ***3ah****, Scheme 2.* The same general procedure was followed by using 2,4,6-trimethoxybenzoic acid (42.5 mg, 0.2 mmol), diethyl 2-allylmalonate (60 μL, 0.3 mmol, 1.5 equiv), palladium(II) trifluoroacetate (13.4 mg, 0.04 mmol, 0.1 equiv), and 1,4-benzoquinone (65 mg, 0.6 mmol, 3.0 equiv). Column chromatography ($SiO_2$, eluting with 8:2 hexane/ethyl acetate) afforded the desired product as a colorless oil, (45 mg, 62%). $^1$H NMR (600 MHz, $CDCl_3$) δ 6.66 (d, *J* = 16.2 Hz, 1H), 6.38−6.43 (m, 1H), 6.12 (s, 2H), 4.18−4.23 (m, 4H), 3.81 (s, 3H), 3.80 (s, 6H), 3.48 (t, *J* = 7.8 Hz, 1H), 2.80 (t, *J* = 7.8 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 6H); $^{13}$C{$^1$H} NMR (150 MHz, $CDCl_3$) δ 169.2, 159.8, 159.0, 127.2, 122.8, 107.7, 90.6, 61.2, 55.6, 55.2, 52.6, 34.0, 14.0; IR (neat) $\upsilon_{max}$ 2939, 1729, 1604, 1462, 1124, 1036, 814 cm$^{-1}$; HRMS (ESI, *m*/*z*) calcd. for $C_{19}H_{26}O_7Na$ [M + Na]$^+$ 389.1576, found 389.1563.

**General Experimental Procedure for the Decarboxylative Heck Reaction between Electron-Deficient Carboxylic Acids and Vinyl Arenes.** To an oven-dried 15 mL sealed tube, a mixture of pentafluorobenzoic acid (0.20−0.24 mmol, 1.0−1.2 equiv), palladium(II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and silver carbonate (110 mg, 0.4 mmol, 2.0 equiv) was taken then dry DMF (3.0 mL) was added to it. After purging with nitrogen, the corresponding styrenes (0.20−0.30 mmol, 1.0−1.5 equiv) were added via microliter syringe and the vessel was sealed with a screw


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cap. The reaction mixture was allowed to stir for 16 h at room temperature. After completion (as detected by TLC), the reaction mixture was poured into water (20 mL) and extracted with ethyl acetate (30 mL). The organic layer was washed with water (10 mL × 2) and brine (10 mL), dried over anhydrous $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography using ethyl acetate/hexane as eluent to afford the desired product.

*1,2,3,4,5-Pentafluoro-6-styrylbenzene,* ***6a****, Scheme 3.*[19] The same general procedure was followed by using pentafluorobenzoic acid (42.5 mg, 0.2 mmol, 1.0 equiv), styrene (35 μL, 0.3 mmol, 1.5 equiv), palladium(II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and silver carbonate (110 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 98:2 hexane/ethyl acetate) afforded the desired product as a white solid, (36 mg, 66%), mp 132−134 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.53 (d, $J$ = 7.5 Hz, 2H), 7.31−7.47 (m, 4H), 6.98 (d, $J$ = 16.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) $\delta$ 144.8 (dm, $J$ = 248.8 Hz), 139.7 (dm, $J$ = 252.8 Hz), 137.7 (dm, $J$ = 248.2 Hz), 137.1 (td, $J$ = 8.2 Hz, 2.6 Hz), 136.4, 128.9, 128.8, 126.8 112.6 (d, $J$ = 2.4 Hz), 112.4 (td, $J$ = 13.6 Hz, 4.2 Hz); $^{19}$F NMR (470 MHz, $CDCl_3$) $\delta$ −146.0 (dd, $J$ = 21.6 Hz, 7.0 Hz, 2F), −159.8 (t, $J$ = 20.7 Hz, 1F), −166.2 (td, $J$ = 20.7 Hz, 7.0 Hz, 2F); IR (neat) $\upsilon_{max}$ 1523, 1493, 1000, 959, 754 cm$^{-1}$; HRMS (EI, $m/z$) calcd. for $C_{14}H_7F_5$ $[M]^+$ 270.0468, found 270.0448.

*1-(4-Fluorostyryl)-2,3,4,5,6-pentafluorobenzene,* ***6b****, Scheme 3.*[19] The same general procedure was followed by using pentafluorobenzoic acid (42.5 mg, 0.2 mmol, 1.0 equiv), 4-fluorostyrene (36 μL, 0.3 mmol, 1.5 equiv), palladium(II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and silver carbonate (110 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 98:2 hexane/ethyl acetate) afforded the desired product as a white solid, (36 mg, 62%), mp 110−112 °C. $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.51 (dd, $J$ = 8.4 Hz, 5.4 Hz, 2H), 7.39 (d, $J$ = 16.8 Hz, 1H), 7.09 (t, $J$ = 8.4 Hz, 2H), 6.89 (d, $J$ = 16.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) $\delta$ 163.1 (d, $J$ = 248.0 Hz), 144.8 (dm, $J$ = 249.0 Hz), 139.7 (dm, $J$ = 253.5 Hz), 137.7 (dm, $J$ = 249.0 Hz), 135.9 (td, $J$ = 9.0 Hz, 1.5 Hz), 132.6 (d, $J$ = 3.0 Hz), 128.5 (d, $J$ = 7.5 Hz), 115.9 (d, $J$ = 22.5 Hz), 112.4, 112.2 (td, $J$ = 13.5 Hz, 4.5 Hz); $^{19}$F NMR (470 MHz, $CDCl_3$) $\delta$ −115.2 (s, 1F), −146.1 (dd, $J$ = 21.2 Hz, 7.5 Hz, 2F), −159.6 (t, $J$ = 20.7 Hz, 1F), −166.1 (td, $J$ = 21.2 Hz, 7.5 Hz, 2F); IR (neat) $\upsilon_{max}$ 1519, 1492, 1240, 1003, 958 cm$^{-1}$; HRMS (EI, $m/z$) calcd. for $C_{14}H_6F_6$ $[M]^+$ 288.0374, found 288.0365.

*1-(4-Chlorostyryl)-2,3,4,5,6-pentafluorobenzene,* ***6c****, Scheme 3.* The same general procedure was followed by using pentafluorobenzoic acid (42.5 mg, 0.2 mmol, 1.0 equiv), 4-chlorostyrene (38 μL, 0.3 mmol, 1.5 equiv), palladium(II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and silver carbonate (110 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 98:2 hexane/ethyl acetate) afforded the desired product as a white solid, (44 mg, 73%), mp 98−100 °C. $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.47 (d, $J$ = 8.4 Hz, 2H), 7.37−7.41 (m, 3H), 6.96 (d, $J$ = 16.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) $\delta$ 144.8 (dm, $J$ = 249.2 Hz), 139.8 (dm, $J$ = 253.5 Hz), 137.8 (dm, $J$ = 249.2 Hz), 135.7 (td, $J$ = 9.0 Hz, 3.0 Hz), 134.9, 134.7, 129.0, 128.0, 113.2 (d, $J$ = 1.5 Hz), 112.0 (td, $J$ = 13.5 Hz, 4.5 Hz); $^{19}$F NMR (470 MHz, $CDCl_3$) $\delta$ −142.6 (dd, $J$ = 22.1 Hz, 7.0 Hz, 2F), −156.0 (t, $J$ = 20.7 Hz, 1F), −162.8 (td, $J$ = 20.7 Hz, 6.6 Hz, 2F) ; IR (neat) $\upsilon_{max}$ 1520, 1490, 1004, 958, 811 cm$^{-1}$; HRMS (EI, $m/z$) calcd. for $C_{14}H_6ClF_5$ $[M]^+$ 304.0078, found 304.0061.

*1-(4-Bromostyryl)-2,3,4,5,6-pentafluorobenzene,* ***6d****, Scheme 3.* The same general procedure was followed by using pentafluorobenzoic acid (42.5 mg, 0.2 mmol, 1.0 equiv), 4-bromostyrene (39 μL, 0.3 mmol, 1.5 equiv), palladium(II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and silver carbonate (110 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 98:2 hexane/ethyl acetate) afforded the desired product as a white solid, (47 mg, 67%), mp 99−101 °C. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.52 (d, $J$ = 8.1 Hz, 2H), 7.34−7.41 (m, 3H), 6.97 (d, $J$ = 16.8 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) $\delta$ 144.7 (dm, $J$ = 248.9 Hz), 139.8 (dm, $J$ = 252.8 Hz), 137.7 (dm, $J$ = 249.8 Hz), 135.8 (td, $J$ = 9.0 Hz, 1.5 Hz), 135.3, 132.0, 128.2, 122.9, 113.3 (d, $J$ = 3.0 Hz), 112.0 (td, $J$ = 13.5 Hz, 4.5 Hz); $^{19}$F NMR (470 MHz, $CDCl_3$) $\delta$ −142.6 (dd, $J$ = 21.2 Hz, 6.6 Hz, 2F), −155.9 (t, $J$ = 21.6 Hz, 1F), −162.7 (td, $J$ = 21.6 Hz, 7.0 Hz, 2F); IR (neat) $\upsilon_{max}$ 1519, 1492, 1002, 961, 810 cm$^{-1}$; HRMS (EI, $m/z$) calcd. for $C_{14}H_6BrF_5$ $[M]^+$ 347.9573, 349.9553, found 347.9570, 349.9529.

*1-(4-Methylstyryl)-2,3,4,5,6-pentafluorobenzene,* ***6e****, Scheme 3.*[13a] The same general procedure was followed by using pentafluorobenzoic acid (42.5 mg, 0.2 mmol, 1.0 equiv), 4-methylstyrene (40 μL, 0.3 mmol, 1.5 equiv), palladium(II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and silver carbonate (110 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 97:3 hexane/ethyl acetate) afforded the desired product as a white solid, (41 mg, 73%), mp 142−144 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.38−7.44 (m, 3H), 7.20 (d, $J$ = 8.1 Hz, 2H), 6.93 (d, $J$ = 16.8 Hz, 1H), 2.38 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) $\delta$ 144.7 (dm, $J$ = 248.3 Hz), 139.5 (dm, $J$ = 252.8 Hz), 139.1, 137.7 (dm, $J$ = 250.5 Hz), 137.1 (td, $J$ = 8.2 Hz, 2.2 Hz), 133.7, 129.5, 126.8, 112.6 (td, $J$ = 13.5 Hz, 4.5 Hz), 111.6 (d, $J$ = 2.2 Hz), 21.3; $^{19}$F NMR (470 MHz, $CDCl_3$) −143.0 (dd, $J$ = 22.6 Hz, 6.1 Hz, 2F), −157.1 (t, $J$ = 20.7 Hz, 1F), −163.2 (td, $J$ = 20.7 Hz, 6.1 Hz, 2F); IR (neat) $\upsilon_{max}$ 2924, 1519, 1492, 1001, 958, 804 cm$^{-1}$; HRMS (EI, $m/z$) calcd. for $C_{15}H_9F_5$ $[M]^+$ 284.0624, found 284.0615.

*1-(4-Ethylstyryl)-2,3,4,5,6-pentafluorobenzene,* ***6f****, Scheme 3.* The same general procedure was followed by using pentafluorobenzoic acid (42.5 mg, 0.2 mmol, 1.0 equiv), 4-ethylstyrene (44 μL, 0.3 mmol, 1.5 equiv), palladium(II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and silver carbonate (110 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 97:3 hexane/ethyl acetate) afforded the desired product as a white solid, (33 mg, 56%), mp 134−136 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.39−7.47 (m, 3H), 7.32 (d, $J$ = 8.1 Hz, 2H), 6.94 (d, $J$ = 16.5 Hz, 1H), 2.67 (q, $J$ = 7.5 Hz, 2H), 1.26 (t, $J$ = 7.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) $\delta$ 144.7 (dm, $J$ = 248.4 Hz), 145.5, 139.5 (dm, $J$ = 252.0 Hz), 137.8 (dm, $J$ = 249.2 Hz), 137.1 (t, $J$ = 8.2 Hz), 134.0, 128.4, 126.9, 112.6 (td, $J$ = 13.5 Hz, 3.8 Hz), 111.7 (d, $J$ = 1.5 Hz), 28.7, 15.4; $^{19}$F NMR (470 MHz, $CDCl_3$) $\delta$ −143.0 (dd, $J$ = 20.2 Hz, 5.2 Hz, 2F), −157.1 (t, $J$ = 20.7 Hz, 1F), −163.2 (td, $J$ = 20.7 Hz, 5.6 Hz, 2F); IR (neat) $\upsilon_{max}$ 2925, 1522, 1491, 1001, 959, 819 cm$^{-1}$; HRMS (EI, $m/z$) calcd. for $C_{16}H_{11}F_5$ $[M]^+$ 298.0781, found 298.0784.

*1-(4-tert-Butylstyryl)-2,3,4,5,6-pentafluorobenzene,* ***6g****, Scheme 3.* The same general procedure was followed by using pentafluorobenzoic acid (51 mg, 0.24 mmol, 1.2 equiv), 4-*tert*-butylstyrene (37 μL, 0.2 mmol, 1.0 equiv), palladium(II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and silver carbonate (110 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 98:2 hexane/ethyl acetate) afforded the desired product as a white solid, (46 mg, 70%), mp 100−102 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.35−7.49 (m, 5H), 6.94 (d, $J$ = 16.8 Hz, 1H), 1.34 (s, 9H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) $\delta$ 152.4, 144.7 (dm, $J$ = 248.2 Hz), 139.5 (dm, $J$ = 252.0 Hz), 137.8 (dm, $J$ = 249.0 Hz), 137.0 (t, $J$ = 8.2 Hz), 133.7, 126.6, 125.8, 122.6 (td, $J$ = 13.5 Hz, 3.8 Hz), 111.8, 34.8, 31.2; $^{19}$F NMR (470 MHz, $CDCl_3$) −142.9 (dd, $J$ = 21.6 Hz, 6.6 Hz, 2F), −157.0 (t, $J$ = 20.7 Hz, 1F), −163.2 (td, $J$ = 21.2 Hz, 6.6 Hz, 2F); IR (neat) $\upsilon_{max}$ 2971, 1520, 1498, 1003, 960, 822 cm$^{-1}$; HRMS (EI, $m/z$) calcd. for $C_{18}H_{15}F_5$ $[M]^+$ 326.1094, found 326.1081.

*1-(4-Methoxystyryl)-2,3,4,5,6-pentafluorobenzene,* ***6h****, Scheme 3.*[19] The same general procedure was followed by using pentafluorobenzoic acid (51 mg, 0.24 mmol, 1.2 equiv), 4-vinylanisole (27 μL, 0.2 mmol, 1.0 equiv), palladium(II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and silver carbonate (110 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 97:3 hexane/ethyl acetate) afforded the desired product as a white solid, (43 mg, 72%), mp 128−130 °C. $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.47 (d, $J$ = 9.0 Hz, 2H), 7.38 (d, $J$ = 16.8 Hz, 1H), 6.92 (d, $J$ = 9.0, 2H), 6.83 (d, $J$ = 16.8 Hz, 1H), 3.85 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) $\delta$ 160.3, 144.6 (dm, $J$ = 247.5 Hz), 139.3 (dm, $J$ = 252.0 Hz), 137.8 (dm, $J$ = 247.5 Hz), 136.6 (td, $J$ = 9.0 Hz, 1.5 Hz), 129.2, 128.2, 114.2, 112.7 (td, $J$ = 13.5 Hz, 4.5 Hz), 110.3 (d, $J$ = 3.0 Hz), 55.3; $^{19}$F NMR (470 MHz, $CDCl_3$) $\delta$ −143.2 (dd, $J$ = 21.2 Hz, 5.2 Hz, 2F), −157.5 (t, $J$ = 20.7 Hz, 1F), −163.3 (td, $J$ = 20.7 Hz, 5.6 Hz, 2F); IR (neat) $\upsilon_{max}$



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2926, 1603, 1519, 1492, 1255, 1001, 956, 816 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{15}H_9OF_5$ $[M]^+$ 300.0574, found 300.0561.

*4-(Perfluorostyryl)phenyl acetate,* ***6i****, Scheme 3.* The same general procedure was followed by using pentafluorobenzoic acid (51 mg, 0.24 mmol, 1.2 equiv), 4-acetoxystyrene (30 μL, 0.2 mmol, 1.0 equiv), palladium(II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and silver carbonate (110 mg, 0.4 mmol, 2.0 equiv). In this case little bit unreacted styrene was there with the same polarity desired products. To purify the desired products high pressure vacuum pump was used to remove the unreacted styrene. Column chromatography ($SiO_2$, eluting with 97:3 hexane/ethyl acetate) afforded the desired product as a white solid, (38 mg, 58%), mp 130−132 °C. $^1H$ NMR (600 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.4 Hz, 2H), 7.41, (d, *J* = 16.8 Hz, 1H), 7.13 (d, *J* = 8.4 Hz, 2H), 6.93 (d, *J* = 16.8 Hz, 1H), 2.3 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 169.3, 151.0, 144.8 (dm, *J* = 249.0 Hz), 139.7 (dm, *J* = 252.0 Hz), 137.7 (dm, *J* = 250.5 Hz), 136.0 (td, *J* = 9.0 Hz, 3.0 Hz), 134.2, 127.9, 122.0, 112.8 (d, *J* = 1.5 Hz), 112.2 (td, *J* = 13.5 Hz, 3.0 Hz), 21.1; $^{19}F$ NMR (470 MHz, $CDCl_3$) δ −142.7 (dd, *J* = 21.6 Hz, 6.1 Hz, 2F), −156.4 (t, *J* = 20.7 Hz, 1F), −162.9 (td, *J* = 20.2 Hz, 5.6 Hz, 2F); IR (neat) $\upsilon_{max}$ 2925, 1761, 1518, 1497, 1197, 1007, 957 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{16}H_9O_2F_5$ $[M]^+$ 328.0523, found 328.0525.

*(4-(Perfluorostyryl)phenoxy)(tert-butyl)dimethylsilane,* ***6j****, Scheme 3.* The same general procedure was followed by using pentafluorobenzoic acid (51 mg, 0.24 mmol, 1.2 equiv), 4-(*tert*-butyldimethylsiloxy)styrene (47 μL, 0.2 mmol, 1.0 equiv), palladium-(II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and silver carbonate (110 mg, 0.4 mmol, 2.0 equiv). Here little bit unreacted styrene was there with the same polarity desired products. To purify the desired products high pressure vacuum pump was used to remove the unreacted styrene. Column chromatography ($SiO_2$, eluting with 97:3 hexane/ethyl acetate) afforded the desired product as a white solid, (54 mg, 68%), mp 116−118 °C. $^1H$ NMR (600 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 16.8 Hz, 1H), 6.86 (d, *J* = 9.0 Hz, 2H), 6.84 (d, *J* = 16.8 Hz, 1H), 1.01 (s, 9H), 0.24 (s, 6H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 156.6, 144.6 (dm, *J* = 248.1 Hz), 139.3 (dm, *J* = 252.0 Hz), 137.7 (dm, *J* = 248.7 Hz), 136.8 (td, *J* = 9.0 Hz, 1.5 Hz), 129.8, 128.2, 120.5, 112.7 (td, *J* = 13.5 Hz, 4.5 Hz), 110.5 (d, *J* = 1.5 Hz), 25.6, 18.2, −4.4; $^{19}F$ NMR (470 MHz, $CDCl_3$) δ −143.2 (dd, *J* = 22.6 Hz, 6.1 Hz, 2F), −157.5 (t, *J* = 20.7 Hz, 1F), −163.3 (td, *J* = 20.7 Hz, 6.6 Hz, 2F); IR (neat) $\upsilon_{max}$ 2858, 1600, 1521, 1492, 1276, 1003, 960, 916 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{20}H_{21}OSiF_5$ $[M]^+$ 400.1282, found 400.1278.

*1-(3-Fluorostyryl)-2,3,4,5,6-pentafluorobenzene,* ***6k****, Scheme 3.* The same general procedure was followed by using pentafluorobenzoic acid (42.5 mg, 0.2 mmol, 1.0 equiv), 3-fluorostyrene (36 μL, 0.3 mmol, 1.5 equiv), palladium(II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and silver carbonate (110 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 98:2 hexane/ethyl acetate) afforded the desired product as a white solid, (35 mg, 61%), mp 82−84 °C. $^1H$ NMR (600 MHz, $CDCl_3$) δ 7.39 (d, *J* = 16.2 Hz, 1H), 7.34−7.37 (m, 1H), 7.29 (d, *J* = 7.8 Hz, 1H), 7.22−7.24 (m, 1H), 7.04 (td, *J* = 8.4 Hz, 1.8 Hz, 1H), 6.98 (d, *J* = 16.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 163.1 (d, *J* = 246.0 Hz), 144.8 (dm, *J* = 249.0 Hz), 139.9 (dm, *J* = 253.5 Hz), 138.7 (d, *J* = 7.5 Hz), 137.8 (dm, *J* = 247.5 Hz), 135.8 (t, *J* = 7.5 Hz), 130.3 (d, *J* = 9.0 Hz), 122.8 (d, *J* = 3.0 Hz), 115.8 (d, *J* = 21.0 Hz), 114.0 (d, *J* = 3.0 Hz), 113.2 (d, *J* = 22.5 Hz), 111.9 (td, *J* = 13.5 Hz, 3.0 Hz); $^{19}F$ NMR (470 MHz, $CDCl_3$) δ −112.8 (s, 1F), −142.4 (dd, *J* = 20.7 Hz, 5.2 Hz, 2F), −155.7 (t, *J* = 20.7 Hz, 1F), −162.7 (m, 2F); IR (neat) $\upsilon_{max}$ 1521, 1494, 1004, 955, 680 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{14}H_6F_6$ $[M]^+$ 288.0374, found 288.0365.

*1-(3-Chlorostyryl)-2,3,4,5,6-pentafluorobenzene,* ***6l****, Scheme 3.* The same general procedure was followed by using pentafluorobenzoic acid (42.5 mg, 0.2 mmol, 1.0 equiv), 3-chlorostyrene (38 μL, 0.3 mmol, 1.5 equiv), palladium(II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and silver carbonate (110 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 98:2 hexane/ethyl acetate) afforded the desired product as a white solid, (43 mg, 71%), mp 74−76 °C. $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.31−7.42 (m, 4H), 6.98 (d, *J* = 16.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 144.9 (dm, *J* = 246.8 Hz), 140.0 (dm, *J* = 256.5 Hz), 138.3, 137.8 (dm, *J* = 251.2 Hz), 135.6 (t, *J* = 8.2 Hz), 134.9, 130.0, 128.8, 126.7, 125.1, 114.1, 111.9 (td, *J* = 13.5 Hz, 4.5 Hz); $^{19}F$ NMR (470 MHz, $CDCl_3$) δ −142.4 (dd, *J* = 21.2 Hz, 5.6 Hz, 2F), −155.6 (t, *J* = 20.7 Hz, 1F), 162.6 (td, *J* = 21.6 Hz, 7.0 Hz, 2F); IR (neat) $\upsilon_{max}$ 1519, 1497, 1003, 964, 782 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{14}H_6ClF_5$ $[M]^+$ 304.0078, found 304.0075.

*1-(3-Bromostyryl)-2,3,4,5,6-pentafluorobenzene,* ***6m****, Scheme 3.* The same general procedure was followed by using pentafluorobenzoic acid (42.5 mg, 0.2 mmol, 1.0 equiv), 3-bromostyrene (39 μL, 0.3 mmol, 1.5 equiv), palladium(II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and silver carbonate (110 mg, 0.4 mmol, 2.0 equiv). Here little bit unreacted styrene was there with the same polarity desired products. To purify the desired products high pressure vacuum pump was used to remove the unreacted styrene. Column chromatography ($SiO_2$, eluting with 98:2 hexane/ethyl acetate) afforded the desired product as a white solid, (42 mg, 60%), mp 76−78 °C. $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.67−7.68 (m, 1H), 7.43−7.48 (m, 2H), 7.36 (d, *J* = 16.8 Hz, 1H), 7.24−7.29 (m, 1H), 6.97 (d, *J* = 16.8 Hz, 1H); $^{13}C\{^1H\}$NMR (75 MHz, $CDCl_3$) δ 144.9 (dm, *J* = 249.4 Hz), 140.0 (dm, *J* = 253.6 Hz), 138.6, 137.8 (dm, *J* = 250.5 Hz), 135.5 (t, *J* = 8.2 Hz), 131.8, 130.3, 129.6, 125.5, 123.0, 114.1, 111.9 (td, *J* = 13.5 Hz, 3.8 Hz); $^{19}F$ NMR (470 MHz, $CDCl_3$) δ −145.6 (dd, *J* = 20.7 Hz, 7.0 Hz, 2F), −158.8 (t, *J* = 20.7 Hz, 1F), −165.9 (td, *J* = 20.7 Hz, 7.0 Hz, 2F); IR (neat) $\upsilon_{max}$ 1521, 1496, 1002, 964, 780 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{14}H_6BrF_5$ $[M]^+$ 347.9573, 349.9553, found 347.9573, 349.9541.

*1-(3-Methylstyryl)-2,3,4,5,6-pentafluorobenzene,* ***6n****, Scheme 3.* The same general procedure was followed by using pentafluorobenzoic acid (42.5 mg, 0.2 mmol, 1.0 equiv), 3-methylstyrene (32 μL, 0.3 mmol, 1.5 equiv), palladium(II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and silver carbonate (110 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 98:2 hexane/ethyl acetate) afforded the desired product as a white solid, (37 mg, 65%), mp 104−106 °C. $^1H$ NMR (600 MHz $CDCl_3$) δ 7.40 (d, *J* = 16.8 Hz, 1H), 7.33−7.34 (m, 2H), 7.29 (t, *J* = 7.2 Hz, 1H), 7.16 (d, *J* = 7.2 Hz, 1H), 6.97 (d, *J* = 16.8 Hz, 1H), 2.40 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 144.8 (dm, *J* = 249.0 Hz), 139.6 (dm, *J* = 253.5 Hz), 138.5, 137.7 (dm, *J* = 249.0 Hz), 137.3 (td, *J* = 9.0 Hz, 3.0 Hz), 136.4, 129.8, 128.7, 127.5, 124.0, 112.43 (td, *J* = 13.5 Hz, 3.0 Hz), 112.40 (d, *J* = 3.0 Hz), 21.4; $^{19}F$ NMR (470 MHz, $CDCl_3$) δ −142.8 (dd, *J* = 21.6 Hz, 7.0 Hz, 2F), −156.8 (t, *J* = 20.7 Hz, 1F), −163.1 (m, 2F); IR (neat) $\upsilon_{max}$ 2924, 1521, 1493, 1000, 962, 783 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{15}H_9F_5$ $[M]^+$ 284.0624, found 284.0598.

*1-(3-Methoxystyryl)-2,3,4,5,6-pentafluorobenzene,* ***6o****, Scheme 3.* The same general procedure was followed by using pentafluorobenzoic acid (51 mg, 0.24 mmol, 1.2 equiv), 3-vinylanisole (28 μL, 0.2 mmol, 1.0 equiv), palladium(II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and silver carbonate (110 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 97:3 hexane/ethyl acetate) afforded the desired product as a white solid, (45 mg, 75%), mp 140−142 °C. $^1H$ NMR (600 MHz, $CDCl_3$) δ 7.40 (d, *J* = 16.8 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 1H), 7.13 (d, *J* = 7.8 Hz, 1H), 7.05 (d, *J* = 1.8 Hz, 1H), 6.97 (d, *J* = 16.8 Hz, 1H), 6.90 (dd, *J* = 7.8 Hz, 1.8 Hz, 1H), 3.86 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 159.9, 144.8 (dm, *J* = 249.0 Hz), 139.7 (dm, *J* = 252.0 Hz), 137.8, 137.7 (dm, *J* = 247.5 Hz), 137.0 (td, *J* = 9.0 Hz, 3.0 Hz), 129.8, 119.5, 114.6, 113.0 (d, *J* = 3.0 Hz), 112.3 (td, *J* = 13.5 Hz, 3.0 Hz), 112.1, 55.3; $^{19}F$ NMR (470 MHz, $CDCl_3$) δ −142.7 (dd, *J* = 22.1 Hz, 6.1 Hz, 2F), −156.5 (t, *J* = 20.7 Hz, 1F), −163.0 (td, *J* = 21.2 Hz, 6.1 Hz, 2F); IR (neat) $\upsilon_{max}$ 1578, 1522, 1495, 1268, 1045, 1002, 965, 778 $cm^{-1}$; HRMS (EI, *m/z*) calcd. for $C_{15}H_9OF_5$ $[M]^+$ 300.0574, found 300.0564.

*1-(3-(Trifluoromethyl)styryl)-2,3,4,5,6-pentafluorobenzene,* ***6p****, Scheme 3.* The same general procedure was followed by using pentafluorobenzoic acid (42.5 mg, 0.2 mmol, 1.0 equiv), 3-trifluoromethylstyrene (45 μL, 0.3 mmol, 1.5 equiv), palladium(II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and silver carbonate (110 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 98:2 hexane/ethyl acetate) afforded the desired product as


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a white solid, (45 mg, 67%), mp 76−78 °C. $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.76 (s, 1H), 7.71 (d, $J$ = 7.8 Hz, 1H), 7.59 (d, $J$ = 7.8 Hz, 1H), 7.52 (t, $J$ = 7.8 Hz, 1H), 7.46 (d, $J$ = 16.2 Hz, 1H), 7.05 (d, $J$ = 16.8 Hz, 1H); $^{13}$C{$^1$H} NMR (150 MHz, $CDCl_3$) $\delta$ 144.9 (dm, $J$ = 249.0 Hz), 140.1 (dm, $J$ = 255.0 Hz), 137.2, 137.8 (dm, $J$ = 251.7 Hz), 135.5 (td, $J$ = 9.0 Hz, 1.5 Hz), 131.4 (q, $J$ = 33.0 Hz), 129.8, 129.3, 123.9 (q, $J$ = 271.5 Hz), 125.4 (q, $J$ = 4.5 Hz), 123.6 (q, $J$ = 3.0 Hz), 114.6 (d, $J$ = 3.0 Hz), 111.7 (td, $J$ = 13.5 Hz, 4.5 Hz); $^{19}$F NMR (470 MHz, $CDCl_3$) $\delta$ −66.1 (s, 1F), −145.6 (dd, $J$ = 21.2 Hz, 7.5 Hz, 2F), −158.6 (t, $J$ = 20.7 Hz, 1F), −165.8 (td, $J$ = 21.2 Hz, 7.5 Hz, 2F); IR (neat) $\upsilon_{max}$ 2924, 1520, 1497, 1331, 1128, 1004, 961, 695 cm$^{-1}$; HRMS (EI, $m/z$) calcd. for $C_{15}H_6F_8$ [M]$^+$ 338.0342, found 338.0343.

*1-(2-Methylstyryl)-2,3,4,5,6-pentafluorobenzene,* ***6q****, Scheme 3.* The same general procedure was followed by using pentafluorobenzoic acid (42.5 mg, 0.2 mmol, 1.0 equiv), 2-methylstyrene (31 μL, 0.3 mmol, 1.5 equiv), palladium(II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and silver carbonate (110 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 98:2 hexane/ethyl acetate) afforded the desired product as a white solid, (34 mg, 60%), mp 112−114 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.68 (d, $J$ = 16.8 Hz, 1H), 7.57−7.61 (m, 1H), 7.19−7.28 (m, 3H), 6.86 (d, $J$ = 16.5 Hz, 1H), 2.42 (s, 3H); $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$) $\delta$ 144.8 (dm, $J$ = 248.2 Hz), 139.7 (dm, $J$ = 252.8 Hz), 137.8 (dm, $J$ = 249.8 Hz), 136.4, 135.7, 135.2 (td, $J$ = 8.2 Hz, 3.0 Hz), 130.6, 128.8, 126.4, 125.3, 113.8 (d, $J$ = 3.0 Hz), 112.6 (td, $J$ = 13.5 Hz, 4.5 Hz), 19.7; $^{19}$F NMR (470 MHz, $CDCl_3$) $\delta$ −143.0 (dd, $J$ = 20.2 Hz, 7.5 Hz, 2F), −156.7 (t, $J$ = 20.7 Hz, 1F), −163.0 (td, $J$ = 21.2 Hz, 7.0 Hz, 2F); IR (neat) $\upsilon_{max}$ 2924, 1522, 1494, 1000, 962, 754 cm$^{-1}$; HRMS (EI, $m/z$) calcd. for $C_{15}H_9F_5$ [M]$^+$ 284.0624, found 284.0620.

*1,3-Dimethoxy-5-(perfluorostyryl)benzene,* ***6r****, Scheme 3.* The same general procedure was followed by using pentafluorobenzoic acid (51 mg, 0.24 mmol, 1.2 equiv), 3,5-dimethoxystyrene (33 μL, 0.2 mmol, 1.0 equiv), palladium(II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and silver carbonate (110 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 97:3 hexane/ethyl acetate) afforded the desired product as a white solid, (46 mg, 69%), mp 103−105 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.36 (d, $J$ = 16.5 Hz, 1H), 6.95 (d, $J$ = 16.8 Hz, 1H), 6.67 (d, $J$ = 2.1 Hz, 2H), 6.46 (t, $J$ = 2.1 Hz, 1H), 3.84 (s, 6H); $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$) $\delta$ 161.1, 144.8 (dm, $J$ = 249.2 Hz), 139.7 (dm, $J$ = 253.0 Hz), 137.7 (dm, $J$ = 249.8 Hz), 138.4, 137.1 (td, $J$ = 8.2 Hz, 1.5 Hz), 113.1 (d, $J$ = 2.2 Hz), 112.2 (td, $J$ = 13.5 Hz, 4.5 Hz), 104.9, 101.1, 55.4; $^{19}$F NMR (470 MHz, $CDCl_3$) $\delta$ −142.6 (dd, $J$ = 20.7 Hz, 5.6 Hz, 2F), −156.4 (t, $J$ = 20.7 Hz, 1F), −163.0 (m, 2F); IR (neat) $\upsilon_{max}$ 1593, 1522, 1494, 1296, 1155, 1061, 1005 cm$^{-1}$; HRMS (EI, $m/z$) calcd. for $C_{16}H_{11}O_2F_5$ [M]$^+$ 330.0679, found 330.0678.

*1-(3,4-Dimethoxystyryl)-2,3,4,5,6-pentafluorobenzene,* ***6s****, Scheme 3.* The same general procedure was followed by using pentafluorobenzoic acid (51 mg, 0.24 mmol, 1.2 equiv), 3,4-dimethoxystyrene (30 μL, 0.2 mmol, 1.0 equiv), palladium(II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and silver carbonate (110 mg, 0.4 mmol, 2.0 equiv). Here little bit unreacted styrene was there with the same polarity desired products. To purify the desired products high pressure vacuum pump was used to remove the unreacted styrene. Column chromatography ($SiO_2$, eluting with 97:3 hexane/ethyl acetate) afforded the desired product as a white solid, (45 mg, 68%), mp 131−133 °C. $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.36 (d, $J$ = 16.2 Hz, 1H), 7.08 (dd, $J$ = 8.4 Hz, 2.4 Hz, 1H), 7.04 (d, $J$ = 1.8 Hz, 1H), 6.87 (d, $J$ = 7.8 Hz, 1H), 6.82 (d, $J$ = 16.8 Hz, 1H), 3.95 (s, 3H), 3.92 (s, 3H); $^{13}$C{$^1$H} NMR (150 MHz, $CDCl_3$) $\delta$ 149.6, 149.2, 144.6 (dm, $J$ = 247.5 Hz), 139.4 (dm, $J$ = 247.5 Hz), 137.7 (dm, $J$ = 247.5 Hz), 136.9 (td, $J$ = 9.0 Hz, 1.5 Hz), 120.6, 112.6 (td, $J$ = 13.5 Hz, 4.5 Hz), 111.1, 110.5 (d, $J$ = 3.0 Hz), 108.8, 55.92, 55.90; $^{19}$F NMR (470 MHz, $CDCl_3$) $\delta$ −143.2 (dd, $J$ = 20.7 Hz, 5.2 Hz, 2F), −157.3 (t, $J$ = 20.7 Hz, 1F), −163.2 (td, $J$ = 20.7 Hz, 5.2 Hz, 2F); IR (neat) $\upsilon_{max}$ 1520, 1494, 1262, 1022, 961 cm$^{-1}$; HRMS (ESI, $m/z$) calcd. for $C_{16}H_{11}O_2F_5Na$ [M + Na]$^+$ 353.0577, found 353.0577.

*2-Methoxy-4-(perfluorostyryl)phenyl acetate,* ***6t****, Scheme 3.* The same general procedure was followed by using pentafluorobenzoic acid (51 mg, 0.24 mmol, 1.2 equiv), 4-acetoxy-3-methoxystyrene (38 μL, 0.2 mmol, 1.0 equiv), palladium(II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and silver carbonate (110 mg, 0.4 mmol, 2.0 equiv). Column chromatography ($SiO_2$, eluting with 97:3 hexane/ethyl acetate) afforded the desired product as a white solid, (44 mg, 62%), mp 149−151 °C. $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.40 (d, $J$ = 16.8 Hz, 1H), 7.12 (dd, $J$ = 8.4 Hz, 1.8 Hz, 1H), 7.09 (s, 1H), 7.06 (d, $J$ = 7.8 Hz, 1H), 6.91 (d, $J$ = 16.8 Hz, 1H), 3.90 (s, 3H), 2.53 (s, 3H); $^{13}$C{$^1$H} NMR (150 MHz, $CDCl_3$) $\delta$ 168.9, 151.3, 144.8 (dm, $J$ = 249.0 Hz), 140.3, 139.7 (dm, $J$ = 252.6 Hz), 137.7 (dm, $J$ = 250.5 Hz), 136.4 (td, $J$ = 9.0 Hz, 1.5 Hz), 135.4, 123.1, 119.6, 112.9 (d, $J$ = 1.5 Hz), 112.2 (td, $J$ = 13.5 Hz, 3.0 Hz), 110.4, 55.9, 20.6; $^{19}$F NMR (470 MHz, $CDCl_3$) $\delta$ −142.7 (dd, $J$ = 20.7 Hz, 5.6 Hz, 2F), −156.3 (t, $J$ = 20.7 Hz, 1F), −162.9 (m, 2F); IR (neat) $\upsilon_{max}$ 1764, 1517, 1496, 1204, 1004, 968 cm$^{-1}$; HRMS (ESI, $m/z$) calcd. for $C_{17}H_{11}O_3F_5Na$ [M + Na]$^+$ 381.0526, found 381.0534.

*1,2,3,4-Tetrafluoro-5-styrylbenzene,* ***6u****, Scheme 3.*[13a] The same general procedure was followed by using 1,2,3,4-tetrafluorobenzoic acid (39 mg, 0.2 mmol, 1.0 equiv), styrene (35 μL, 0.3 mmol, 1.5 equiv), palladium(II) trifluoroacetate (13.4 mg, 0.04 mmol, 0.2 equiv), and silver carbonate (165 mg, 0.6 mmol, 3.0 equiv). 5% DMSO was used as a co solvent and the reaction was run for 4 h at 120 °C. Column chromatography ($SiO_2$, eluting with 98:2 hexane/ethyl acetate) afforded the desired product as a white solid, (30 mg, 60%), mp 86−88 °C. $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.52 (d, $J$ = 7.8 Hz, 2H), 7.39 (t, $J$ = 7.8 Hz, 2H), 7.33 (t, $J$ = 7.8 Hz, 1H), 7.18−7.22 (m, 1H), 7.08−7.15 (m, 2H); $^{13}$C{$^1$H} NMR (150 MHz, $CDCl_3$) $\delta$ 147.3 (dm, $J$ = 244.8 Hz), 145.3 (dm, $J$ = 248.4 Hz), 141.0 (dm, $J$ = 250.0 Hz), 139.6 (dm, $J$ = 252.9 Hz), 136.1, 132.9 (t, $J$ = 3.0 Hz), 128.8, 128.7, 126.8, 121.7 (m), 117.9 (t, $J$ = 3.0 Hz), 107.4 (dt, $J$ = 21.0 Hz, 3.0 Hz); $^{19}$F NMR (470 MHz, $CDCl_3$) $\delta$ −139.8 (dd, $J$ = 21.2 Hz, 11.3 Hz, 1F), −144.1 (dd, $J$ = 20.7 Hz, 10.8 Hz, 1F) −156.0 (t, $J$ = 19.3 Hz, 1F), −157.0 (t, $J$ = 20.7 Hz, 1F); IR (neat) $\upsilon_{max}$ 1527, 1477, 1039, 942, 756, 693 cm$^{-1}$; HRMS (EI, $m/z$) calcd. for $C_{14}H_8F_4$ [M]$^+$ 252.0562, found 252.0556.

*1-(2,6-Difluorostyryl)benzene,* ***6v****, Scheme 3.*[13a] The same general procedure was followed by using 2,6-difluorobenzoic acid (32 mg, 0.2 mmol, 1.0 equiv), styrene (35 μL, 0.3 mmol, 1.5 equiv), palladium(II) trifluoroacetate (13.4 mg, 0.04 mmol, 0.2 equiv), and silver carbonate (165 mg, 0.4 mmol, 3.0 equiv). 5% DMSO was used as a co solvent and the reaction was run for 4 h at 120 °C. Column chromatography ($SiO_2$, eluting with 98:2 hexane/ethyl acetate) afforded the desired product as a white solid, (30 mg, 70%), mp 65−67 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.54 (d, $J$ = 7.2 Hz, 2H), 7.25−7.42 (m, 4H), 7.11−7.18 (m, 2H), 6.91 (t, $J$ = 8.4 Hz, 2H); $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$) $\delta$ 161.0 (dm, $J$ = 249.8 Hz), 137.4, 135.1 (t, $J$ = 8.1 Hz), 128.7, 128.2, 127.8 (t, $J$ = 10.5 Hz), 126.7, 115.2, 114.8 (t, $J$ = 15.0 Hz), 111.5 (m); $^{19}$F NMR (470 MHz, $CDCl_3$) $\delta$ −113.0 (s, 2F); IR (neat) $\upsilon_{max}$ 1565, 1463, 1210, 993, 748 cm$^{-1}$.

*1-Cinnamyl-2,3,4,5,6-pentafluorobenzene,* ***6w****, Scheme 3.*[28] The same general procedure was followed by using pentafluorobenzoic acid (42.5 mg, 0.2 mmol, 1.0 equiv), allylbenzene (40 μL, 0.3 mmol, 1.5 equiv), palladium(II) trifluoroacetate (6.7 mg, 0.02 mmol, 0.1 equiv), and silver carbonate (110 mg, 0.4 mmol, 2.0 equiv) except the reaction was run at 120 °C. Column chromatography ($SiO_2$, eluting with 98:2 hexane/ethyl acetate) afforded the desired product as a colorless liquid, (42 mg, 74%). $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.23−7.36 (m, 5H), 6.50 (d, $J$ = 15.6 Hz, 1H), 6.21−6.26 (m, 1H), 3.62 (dd, $J$ = 6.6 Hz, 0.6 Hz, 2H); $^{13}$C{$^1$H} NMR (150 MHz, $CDCl_3$) $\delta$ 145.0 (dm, $J$ = 244.5 Hz), 139.8 (dm, $J$ = 250.5 Hz), 137.5 (dm, $J$ = 249.0 Hz), 136.5, 132.4, 128.6, 127.6, 126.2, 124.2, 113.2 (td, $J$ = 19.5 Hz, 4.5 Hz), 25.6; $^{19}$F NMR (470 MHz, $CDCl_3$) $\delta$ −143.9 (dd, $J$ = 21.6 Hz, 7.0 Hz, 2F), −157.3 (t, $J$ = 20.7 Hz, 1F), −162.5 (td, $J$ = 20.7 Hz, 7.0 Hz, 2F); IR (neat) $\upsilon_{max}$ 1498, 1118, 990, 963, 911, 754, 694 cm$^{-1}$; HRMS (EI, $m/z$) calcd. for $C_{15}H_9F_5$ [M]$^+$ 284.0624, found 284.0608.

*Gram Scale Reaction: (Synthesis of 1,2,3,4,5-Pentafluoro-6-styrylbenzene, Scheme 3,* ***6a****).* To an oven-dried 250 mL round-bottom flask, a mixture of pentafluorobenzoic acid (1.0 g, 4.7 mmol, 1.0 equiv), palladium(II) trifluoroacetate (156 mg, 0.47 mmol, 0.1 equiv), and silver carbonate (2.6 g, 9.4 mmol, 2.0 equiv) was taken then dry DMF (80 mL) was added to it under nitrogen atmosphere.



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To this reaction mixture styrene (0.8 mL, 7.05 mmol,) was added via syringe. The reaction mixture was allowed to stir for 16 h at room temperature under nitrogen atmosphere. After completion (as detected by TLC), the reaction mixture was poured into water (60 mL) and extracted with ethyl acetate (80 mL). The organic layer was washed with water (30 mL) and brine (20 mL), dried over anhydrous $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The pure 1,2,3,4,5-pentafluoro-6-styrylbenzene (**6a**) was obtained as a white solid in 61% (775 mg) yield after column chromatography of the crude reaction mixture using ethyl acetate/hexane (98:2) as eluent.

*Experimental Procedure for the Preparation of 1-(2,3,5,6-Tetrafluoro-4-styrylphenyl)-1H-indole,* ***7****, Scheme 6 from 1,2,3,4,5-Pentafluoro-6-styrylbenzene (****6a****).* Sodium *tert*-butoxide (53 mg, 0.55 mmol, 1.1 equiv) was added to a glass vial containing indole (59 mg, 0.5 mmol, 1.0 equiv) in dry DMA (3.0 mL). The mixture was stirred at room temperature for 1.0 min. The mixture was cooled and added to a cooled solution of 1,2,3,4,5-pentafluoro-6-styrylbenzene (162 mg, 0.6 mmol,1.2 equiv) in dry DMA (3.0 mL) under stirring in a 10 mL round-bottom flask. After 15 min the cooling bath was removed and the reaction mixture was allowed to stir for 1 h at room temperature under nitrogen atmosphere. After completion (as detected by TLC), the reaction mixture was mixed with sat. $NH_4Cl$ (aq.) (5.0 mL) and water (10 mL) then extracted with ethyl acetate (20 mL) The organic layer was washed with water (10 mL) and brine (10 mL), dried over anhydrous $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography eluting with hexane/ethyl acetate (8:2) afforded the desired product as a white solid, (156 mg, 85%), mp 130−132 °C. $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.75 (d, $J$ = 7.8 Hz, 1H), 7.61−7.64 (m, 3H), 7.46 (t, $J$ = 7.8 Hz, 2H), 7.40 (t, $J$ = 7.2 Hz, 1H), 7.33 (td, $J$ = 8.4 Hz, 1.2 Hz, 1H), 7.28 (td, $J$ = 7.8 Hz, 1.2 Hz, 1H), 7.23−7.26 (m, 2H), 7.18 (d, $J$ = 16.8 Hz, 1H), 6.83 (d, $J$ = 3.6 Hz, 1H); $^{13}$C{$^1$H} NMR (150 MHz, $CDCl_3$) $\delta$ 145.0 (dm, $J$ = 249.2 Hz), 142.8 (dm, $J$ = 250.0 Hz), 138.0 (t, $J$ = 9.0 Hz), 136.4, 136.3, 129.2, 128.9, 128.7, 128.3, 127.1, 123.1, 121.2 (d, $J$ = 3.0 Hz), 116.6 (m), 116.2 (t, $J$ = 13.5 Hz), 113.2, 110.6, 105.5; $^{19}$F NMR (470 MHz, $CDCl_3$) $\delta$ −145.6 (m, 2F), −150.7 (m, 2F); IR (neat) $\upsilon_{max}$ 1519, 1487, 1204, 971, 748, 693 cm$^{-1}$; HRMS (FAB, $m/z$) calcd. for $C_{22}H_{14}NF_4$ $[M + H]^+$ 368.1062, found 368.1062.

*Experimental Procedure for the Preparation of 1-(2,3,5,6-Tetra(1H-pyrazol-1-yl)-4-styrylphenyl)-1H-indole,* ***8****, Scheme 6 from 1-(2,3,5,6-Tetrafluoro-4-styrylphenyl)-1H-indole (****7****).* Sodium *tert*-butoxide (48 mg, 0.5 mmol, 5.0 equiv) was added to a glass vial containing pyrazole (34 mg, 0.5 mmol, 5.0 equiv) in dry DMA (1.0 mL). The mixture was stirred at room temperature for 1.0 min. The mixture was cooled and added to a cooled solution of 1-(2,3,5,6-tetrafluoro-4-styrylphenyl)-1*H*-indole (37 mg, 0.1 mmol, 1.0 equiv) in dry DMA (1.0 mL) under stirring in a 10 mL round-bottom flask. After 15 min the cooling bath was removed and the reaction mixture was allowed to stir for 1 h at room temperature under nitrogen atmosphere. After completion (as detected by TLC), the reaction mixture was quenched with sat. $NH_4Cl$ (aq.) (1.0 mL) then extracted with ethyl acetate (20 mL) and water (10 mL). The organic layer was washed with water (10 mL) and brine (10 mL), dried over anhydrous $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography eluting with hexane/ethyl acetate (7:3) afforded the desired product as a white solid, (55 mg, 98%), mp 280−282 °C. $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.66 (d, $J$ = 1.8 Hz, 2H), 7.53 (d, $J$ = 2.4 Hz, 2H), 7.42−7.43 (m, 1H), 7.27−7.28 (m, 2H), 7.23−7.24 (m, 3H), 7.00−7.05 (m, 7H), 6.84 (d, $J$ = 3.0 Hz, 1H), 6.41 (d, $J$ = 3.0 Hz, 1H), 6.38 (d, $J$ = 16.8 Hz, 1H), 6.35 (t, $J$ = 1.8 Hz, 2H), 5.90 (t, $J$ = 1.8 Hz, 2H), 5.86 (d, $J$ = 16.8 Hz, 1H); $^{13}$C{$^1$H} NMR (150 MHz, $CDCl_3$) $\delta$ 141.12, 141.10, 138.4, 137.17, 137.16, 136.9, 136.33, 136.28, 132.7, 132.5, 131.3, 128.8, 128.6, 128.3, 127.9, 126.8, 122.4, 120.5, 117.7, 109.6, 107.2, 106.8, 104.8; IR (neat) $\upsilon_{max}$ 2923, 1519, 1480, 1389, 1037, 950, 756 cm$^{-1}$; HRMS (EI, $m/z$) calcd. for $C_{34}H_{25}N_9$ $[M]^+$ 559.2233, found 559.2235.

*Experimental Procedure for the Preparation of Benzyl(2,3,5,6-tetrafluoro-4-styrylphenyl)sulfane,* ***9****, Scheme 6 from 1,2,3,4,5-Pentafluoro-6-styrylbenzene (****6a****).* A mixture of 1,2,3,4,5-pentafluoro-6-styrylbenzene (27 mg, 0.1 mmol, 1.0 equiv), phenylmethanethiol (14 $\mu$L, 0.12 mmol, 1.2 equiv) and TRIS (145 mg, 1.2 mmol, 12 equiv) in dry DMF (2.0 mL) was stirred for 12 h at room temperature under argon atmosphere in a 10 mL round-bottom flask. After completion (as detected by TLC), the reaction mixture was poured into water (10 mL) and extracted with ethyl acetate (20 mL). The organic layer was washed with water (10 mL) and brine (10 mL), dried over anhydrous $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography eluting with hexane/ethyl acetate (8:2) to afford the desired product as a white solid, (34 mg, 90%), mp 108−110 °C. $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.56 (d, $J$ = 7.8 Hz, 2H), 7.50 (d, $J$ = 16.8 Hz, 1H), 7.42 (t, $J$ = 7.2 Hz, 2H), 7.36 (t, $J$ = 7.8 Hz, 1H), 7.25−7.31 (m, 5H), 7.06 (d, $J$ = 16.8 Hz, 1H), 4.16 (s, 2H); $^{13}$C{$^1$H} NMR (150 MHz, $CDCl_3$) $\delta$ 147.1 (dm, $J$ = 242.8 Hz), 144.4 (dm, $J$ = 250.2 Hz), 137.6 (t, $J$ = 9.0 Hz), 136.5 (d, $J$ = 1.5 Hz), 129.0, 128.83, 128.78, 128.6, 127.7, 127.0, 117.0 (t, $J$ = 13.5 Hz), 113.7, 111.4 (t, $J$ = 21.0 Hz), 39.0 (t, $J$ = 3.0 Hz); $^{19}$F NMR (470 MHz, $CDCl_3$) $\delta$ −138.4 (dd, $J$ = 22.6 Hz, 11.3 Hz, 2F), −146.2 (dd, $J$ = 22.6 Hz, 11.3 Hz, 2F); IR (neat) $\upsilon_{max}$ 1468, 1064, 959, 752, 693 cm$^{-1}$; HRMS (EI, $m/z$) calcd. for $C_{21}H_{14}SF_4$ $[M]^+$ 374.0752, found 374.0734.

*Experimental Procedure for the Preparation of tert-Butyl (S)-1-(methoxycarbonyl)-2-(2,3,5,6-tetrafluoro-4-styrylphenylthio)-ethylcarbamate,* ***10****, Scheme 6 from 1,2,3,4,5-Pentafluoro-6-styrylbenzene (****6a****).* A mixture of 1,2,3,4,5-pentafluoro-6-styrylbenzene, **6a** (27 mg, 0.1 mmol, 1.0 equiv), *N*-(*tert*-butoxycarbonyl)-L-cysteine methyl ester (21 $\mu$L, 0.1 mmol, 1.0 equiv) and TRIS (25 mg, 0.2 mmol, 2.0 equiv) in dry DMF (2.0 mL) was stirred for 4.5 h at room temperature under argon atmosphere in a 10 mL round-bottom flask. After completion (as detected by TLC), the reaction mixture was poured into water (10 mL) and extracted with ethyl acetate (20 mL). The organic layer was washed with water (10 mL) and brine (10 mL), dried over anhydrous $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography eluting with hexane/ethyl acetate (7:3) to afford the desired product as a white solid, (41 mg, 84%), mp 90−92 °C. $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.56 (d, $J$ = 7.2 Hz, 2H), 7.52 (d, $J$ = 16.2 Hz, 1H), 7.42 (t, $J$ = 7.2 Hz, 2H), 7.36 (t, $J$ = 7.2 Hz, 1H), 7.08 (d, $J$ = 16.8 Hz, 1H), 5.39 (d, $J$ = 6.6 Hz, 1H), 4.58−4.60 (m, 1H), 3.70 (s, 3H), 3.47 (dd, $J$ = 14.4 Hz, 4.2 Hz, 1H), 3.38 (dd, $J$ = 14.4 Hz, 4.2 Hz, 1H), 1.41 (s, 9H); $^{13}$C{$^1$H} NMR (150 MHz, $CDCl_3$) $\delta$ 170.4, 154.7, 147.1(dm, $J$ = 243.0 Hz), 144.4 (dm, $J$ = 250.5 Hz), 138.0 (t, $J$ = 9.0 Hz), 136.4, 129.1, 128.8, 127.0, 117.5 (t, $J$ = 13.5 Hz), 113.5, 111.0 (t, $J$ = 21.0 Hz), 80.3, 53.7, 52.6, 36.6, 28.1; $^{19}$F NMR (470 MHz, $CDCl_3$) $\delta$ −134.5 (m, 2F), −142.6 (m, 2F); IR (neat) $\upsilon_{max}$ 1739, 1706, 1472, 1342, 1160, 1063, 1015, 963, 754 cm$^{-1}$; HRMS (EI, $m/z$) calcd. for $C_{23}H_{23}NO_4SF_4$ $[M]^+$ 485.1284, found 485.1287.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00100.

$^1$H, $^{13}$C and $^{19}$F NMR spectra. (PDF)

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### Notes

The authors declare no competing financial interest.

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# Palladium-catalyzed decarboxylative, decarbonylative and dehydrogenative C(sp$^2$)–H acylation at room temperature†

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Over the past few decades, an impressive array of C–H activation methodology has been developed for organic synthesis. However, due to the inherent inertness of the C–H bonds (*e.g.* ~110 kcal mol$^{-1}$ for the cleavage of C(aryl)–H bonds) harsh reaction conditions have been realized to overcome high energetic transition states resulting in a limited substrate scope and functional group tolerance. Therefore, the development of mild C–H functionalization protocols is in high demand to exploit the full potential of the C–H activation strategy in the synthesis of a complex molecular framework. Although, electron-rich substrates undergo electrophilic metalation under relatively mild conditions, electron-deficient substrates proceed through a rate-limiting C–H insertion under forcing conditions at high temperature. In addition, a stoichiometric amount of toxic silver salt is frequently used in palladium catalysis to facilitate the C–H activation process which is not acceptable from the environmental and industrial standpoint. We report herein, a Pd(II)-catalyzed decarboxylative C–H acylation of 2-arylpyridines with α-ketocarboxylic acids under mild conditions. The present protocol does not require stoichiometric silver(I) salts as additives and proceeds smoothly at ambient temperature. A novel decarbonylative C–H acylation reaction has also been accomplished using aryl glyoxals as acyl surrogates. Finally, a practical C–H acylation *via* a dehydrogenative pathway has been demonstrated using commercially available benzaldehydes and aqueous hydroperoxides. We also disclose that acetonitrile solvent is optimal for the acylation reaction at room temperature and has a prominent role in the reaction outcome. Control experiments suggest that the acylation reaction *via* decarboxylative, decarbonylative and dehydrogenative proceeds through a radical pathway. Thus we disclose a practical protocol for the sp$^2$ C–H acylation reaction.

## Introduction

Owing to the prevalence of benzophenones in natural products, pharmaceuticals and functionalized materials, the synthesis of functionalized carbonyl compounds is a sustained exertion in organic synthesis (Fig. 1).[1] Typically, Lewis-acid promoted Friedel–Crafts acylation *via* electrophilic aromatic substitution generates isomeric mixtures and requires stoichiometric metal salts.[2] The reaction of Weinreb amides with Grignard reagents yields the carbonyl compounds with limited functional group tolerance,[3] whereas transition metal catalyzed cross-couplings are reported with relatively less nucleophilic organometallic reagents such as organozinc reagents and boronic acids.[4] As an alternative to air and moisture sensitive acyl chlorides which generate stoichiometric metal halide waste, thioesters are used in palladium-catalyzed Liebeskind–Srogl cross-coupling.[5] However, the reaction requires a stoichiometric amount of copper complex as an additive. Carbonylation of aryl halides with hazardous carbon

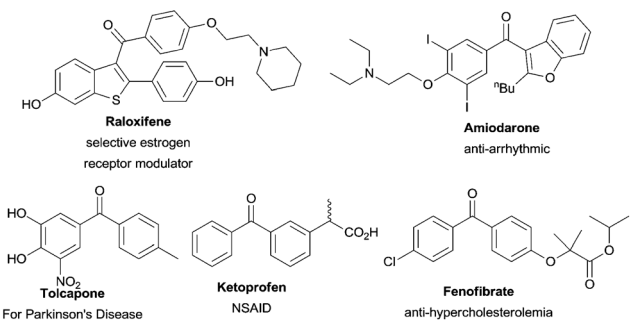


**Fig. 1** Some benzophenone containing drugs.

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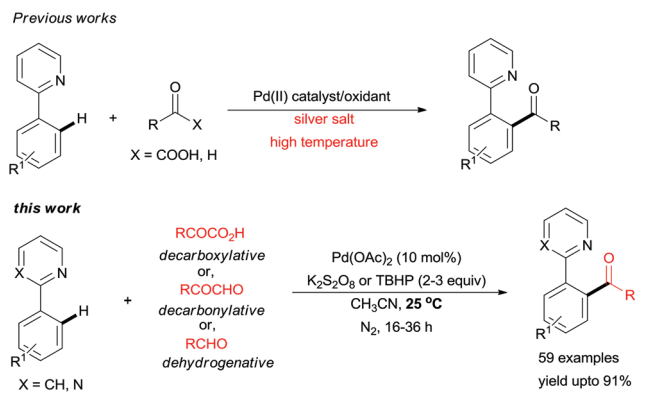
monoxide requires special handling skills and laboratory set up.[6] Therefore, considering the stringent environmental factors (E factors) in chemical processes there is an urgent need for the development of practical and environmentally benign acylation reactions.

Beyond typical cross-coupling approaches, the C–H activation strategy offers a unique opportunity to access carbonyl compounds without prefunctionalization steps.[7] Although an enormous effort has been dedicated for the development of C–H activation processes, significant challenges still remain unsolved. The harsh reaction conditions, use of stoichiometric toxic silver(I) salts, high reaction temperature *etc*. limit their application in the synthesis of complex molecular architecture and industrial processes. Thus, the development of mild acylation reaction *via* C–H activation processes is in high demand.[8]

In recent years, decarboxylative cross-coupling has also been established as a modern strategy for C–C and C–heteroatom bond formation.[9] Inexpensive and readily available carboxylic acids are used as an alternative to expensive organometallic reagents and halides. Combining these two promising technologies, decarboxylative C–H functionalization has emerged as a fascinating field of research.[10] However, like C–H insertion, decarboxylative metalation is also a high energetic process and proceeds at elevated temperatures.[11] α-Oxocarboxylic acids undergo transition metal-catalyzed decarboxylation to provide an acyl anion equivalent which has been utilized in cross-coupling[12] and C–H acylation reaction to provide diaryl ketones.[13] Although decarboxylative C–H acylation of electron rich aniline derivatives or oximes proceeds at ambient temperature through a facile electrophilic *ortho* metalation,[14] electron-deficient substrates require high temperature (110–140 °C) and stoichiometric silver(I) salt which is not acceptable from the environmental and industrial viewpoint.[15] To the best of our knowledge, silver free decarboxylative acylation of electron-deficient 2-arylpyridine at room temperature has not been reported so far. As a part of our continuing research program for the development of cross-coupling reactions under mild conditions, we have reported decarboxylative Heck coupling at room temperature[16] and divergent synthesis of 2-arylindoles and indolines *via* C–H activation.[17] Herein for the first time, we report a palladium-catalyzed decarboxylative C–H acylation of an electron-deficient 2-arylpyridine system at room temperature. The present protocol does not require stoichiometric silver(I) salt and a dramatic influence of the solvent was observed where acetonitrile was found to be optimal for this acylation reaction under ambient conditions.[18] This room temperature acylation reaction was also demonstrated using phenylglyoxals and aldehydes as acylating agents *via* decarbonylative and dehydrogenative manifolds respectively (Scheme 1).

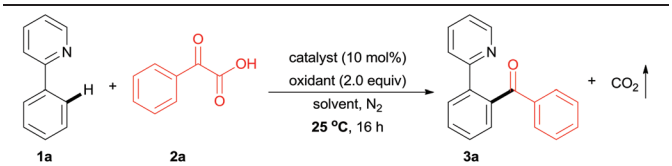



**Scheme 1** C(sp²)–H acylation reaction.

## Results and discussion

Initially, we started optimization for the decarboxylative acylation reaction at room temperature. A mixture of 2-phenylpyridine (**1a**) and phenylglyoxylic acid (**2a**) was stirred in the presence of 10 mol% palladium(II)acetate and 2.0 equiv. of potassium persulfate ($K_2S_2O_8$) in diglyme solvent.[10k] The expected monoacylated product (**3a**) was obtained in 20% yield without any silver(I) salt added (entry 1, Table 1). Further screening of solvents showed that acetonitrile is superior to other solvents such as DMF, DMSO, toluene, acetic acid, 1,4-dioxane and DCE (entries 2–7, Table 1). Typically, silver salt is used in

**Table 1** Optimization of the reaction conditions[a,b]

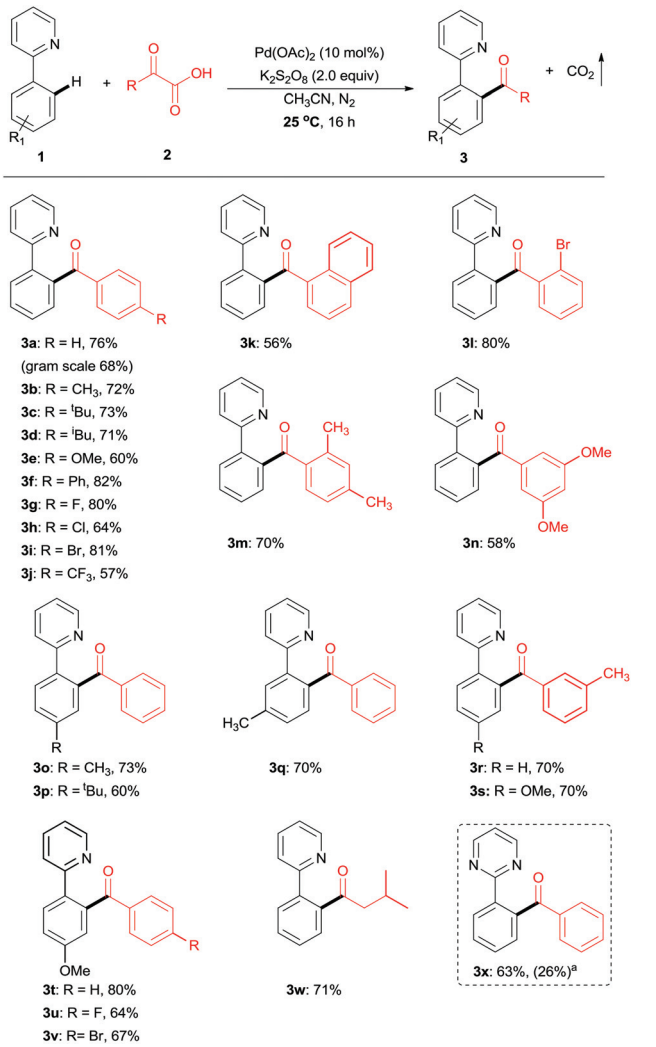



| Entry | Catalyst (10 mol%) | Oxidant (2.0 equiv.) | Solvent | Yield[b] (%) |
|---|---|---|---|---|
| 1 | $Pd(OAc)_2$ | $K_2S_2O_8$ | Diglyme | 20 |
| 2 | $Pd(OAc)_2$ | $K_2S_2O_8$ | DMF | 50 |
| 3 | $Pd(OAc)_2$ | $K_2S_2O_8$ | DMSO | 52 |
| 4 | $Pd(OAc)_2$ | $K_2S_2O_8$ | Toluene | Trace |
| 5 | $Pd(OAc)_2$ | $K_2S_2O_8$ | AcOH | 25 |
| 6 | $Pd(OAc)_2$ | $K_2S_2O_8$ | 1,4-Dioxane | 14 |
| 7 | $Pd(OAc)_2$ | $K_2S_2O_8$ | DCE | 40 |
| **8** | **$Pd(OAc)_2$** | **$K_2S_2O_8$** | **MeCN** | **76** |
| 9 | $Pd(OAc)_2$ | $Ag_2CO_3$ | MeCN | 0 |
| 10 | $Pd(OAc)_2$ | $Ag_2O$ | MeCN | 0 |
| 11 | $Pd(OAc)_2$ | $(NH_4)_2S_2O_8$ | MeCN | 50 |
| 12 | $Pd(OAc)_2$ | PIDA | MeCN | 26 |
| 13 | $Pd(OAc)_2$ | TBHP (in decane) | MeCN | 0 |
| 14 | $Pd(OAc)_2$ | $O_2$ | MeCN | 0 |
| 15 | $Pd(TFA)_2$ | $K_2S_2O_8$ | MeCN | 70 |
| 16 | $Pd(MeCN)_2Cl_2$ | $K_2S_2O_8$ | MeCN | 8 |
| 17 | $Pd(MeCN)_2(OTs)_2$ | $K_2S_2O_8$ | MeCN | 65 |
| 18 | $Pd(MeCN)_4(BF4)_2$ | $K_2S_2O_8$ | MeCN | 57 |
| 19 | $AgNO_3$ | $K_2S_2O_8$ | MeCN | 0 |
| 20 | $Pd(OAc)_2$ | — | MeCN | 0 |
| 21 | — | $K_2S_2O_8$ | MeCN | 0 |
| 22[c] | $Pd(OAc)_2$ | $K_2S_2O_8$ | MeCN | 67 |
| 23[d] | $Pd(OAc)_2$ | $K_2S_2O_8$ | MeCN | 0 |

[a] All reactions were carried out on a 0.1 mmol scale, using **1a** (1.0 equiv.) and **2a** (1.5 equiv.). [b] Yields referred to here are overall isolated yields. [c] Reaction was run in air. [d] Reaction was run under $O_2$.

palladium catalysis for facile decarboxylation, and as a carbonate or carboxylate anion source, halide scavenger and terminal oxidant for catalytic turnover.[19] However, contrary to our expectations, no desired product was isolated using silver salts such as $Ag_2CO_3$, $Ag_2O$ *etc*. at room temperature although it is used as an additive for this transformation at high temperature[15a] (entries 9 and 10, Table 1). Other common oxidants such as ammonium persulfate, (diacetoxyiodo)benzene (PIDA), *tert*-butyl hydroperoxide (in decane) and also molecular oxygen were found to be inferior for this coupling reaction (entries 11–14, Table 1). Owing to the facile electrophilic palladation of cationic palladium salts, several Pd-complexes, such as $Pd(TFA)_2$, $Pd(MeCN)_2Cl_2$, $Pd(MeCN)_2(OTs)_2$, and $Pd(MeCN)_4(BF_4)_2$ were examined but provided a lower yield (entries 15–18, Table 1). We also observed that silver nitrate as a catalyst was inactive for this transformation (entry 19, Table 1). Finally, in combination of 10 mol% $Pd(OAc)_2$ and 2.0 equiv. of $K_2S_2O_8$ as the oxidant using acetonitrile as a solvent provided excellent yield after stirring for 16 h at room temperature (entry 8, Table 1). It is important to note that both $Pd(OAc)_2$ and $K_2S_2O_8$ are essential for this coupling reaction since no desired product was isolated while they were used separately (entries 20 and 21, Table 1). The yield of the acylation product was decreased to some extent in air (entry 22, Table 1) and no product was formed with oxygen purging (entry 23, Table 1). During optimization, it was found that moisture has a negative impact on the reaction outcome presumably due to the formation of a decarboxylative protonation product from phenylglyoxylic acid.

Next we explored the substrate scope under the optimized reaction conditions. A wide variety of phenylglyoxylic acids having electron-withdrawing and electron-donating substituents underwent decarboxylative coupling providing high to excellent yields (Scheme 2). Besides methoxy, alkyl, and aryl groups, halogens such as bromo (**3i**, **3l**, **3v**, Scheme 2), chloro (**3h**, Scheme 2), and fluoro (**3g**, Scheme 2) were also well tolerated under the reaction conditions which are useful for further cross-coupling reactions. A strong electron-withdrawing group on α-keto acid afforded the acylated product in good yield (**3j**, Scheme 3). Interestingly, the α-keto acid with a naphthyl moiety furnished the desired product in good yield (**3k**, Scheme 2). The *ortho* substituted α-keto acid participated in the reaction with excellent yield (**3l**, Scheme 2). Disubstituted α-keto acids also participated in the reaction providing good yields (**3m–3n**, Scheme 2). No significant influence of the electronic nature of the substituents on α-keto acids was observed on the reaction outcome. Similarly, substitutions on the 2-phenylpyridine moiety such as alkyl (**3o–3q**, Scheme 2) and methoxy (**3s–3v**, Scheme 2) were tolerated under the reaction conditions. In addition, aliphatic α-oxocarboxylic acid also afforded the desired product in good yield (**3w**, Scheme 2). Unfortunately, electron deficient groups like acyl and trifluoromethyl on the 2-phenylpyridine moiety did not furnish any acylated products. Other nitrogen directing groups like 2-phenoxypyridine, 1-phenyl-1*H*-pyrazole, acetophenone *O*-methyl oxime, and also 2-phenylbenzo[*d*]thiazole did not provide the

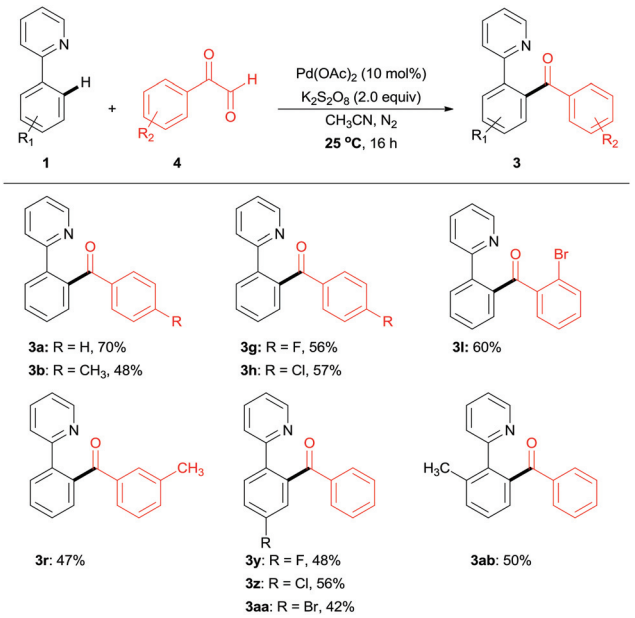



**Scheme 2** Substrate scope of 2-phenylpyridines and α-ketocarboxylic acids. The reaction was carried out on a 0.2 mmol scale, using **1** (1.0 equiv.) and **2** (1.5–2.0 equiv.). The yield referred to here is the average isolated yield of at least two experiments. [a] Diacylation occurred.

desired acylation products at room temperature. However, 2-phenylpyrimidine furnished a mixture of mono and diacylation products which was separated through column chromatography (mono : di = 2.5 : 1). To demonstrate the practical utility of this present protocol the reaction was performed on a gram-scale providing the acylation product in comparable yields (**3a**, Scheme 2).

In recent years, decarbonylative cross-coupling reaction from carbonyl or carboxylic acid derivatives has emerged as a promising strategy in organic synthesis.[20] Initially, the transition metal undergoes oxidative addition to the activated carboxylic acid derivatives such as acid chlorides,[21] anhydrides,[22] esters[23] *etc*. to generate an acyl-metal species. Subsequently, aryl-metal species is formed through the extrusion of carbon monoxide. Unlike redox-neutral decarboxylative cross-coupling, no stoichiometric oxidant is required in the decarbonylative cross-coupling process. Although transition metal-catalyzed

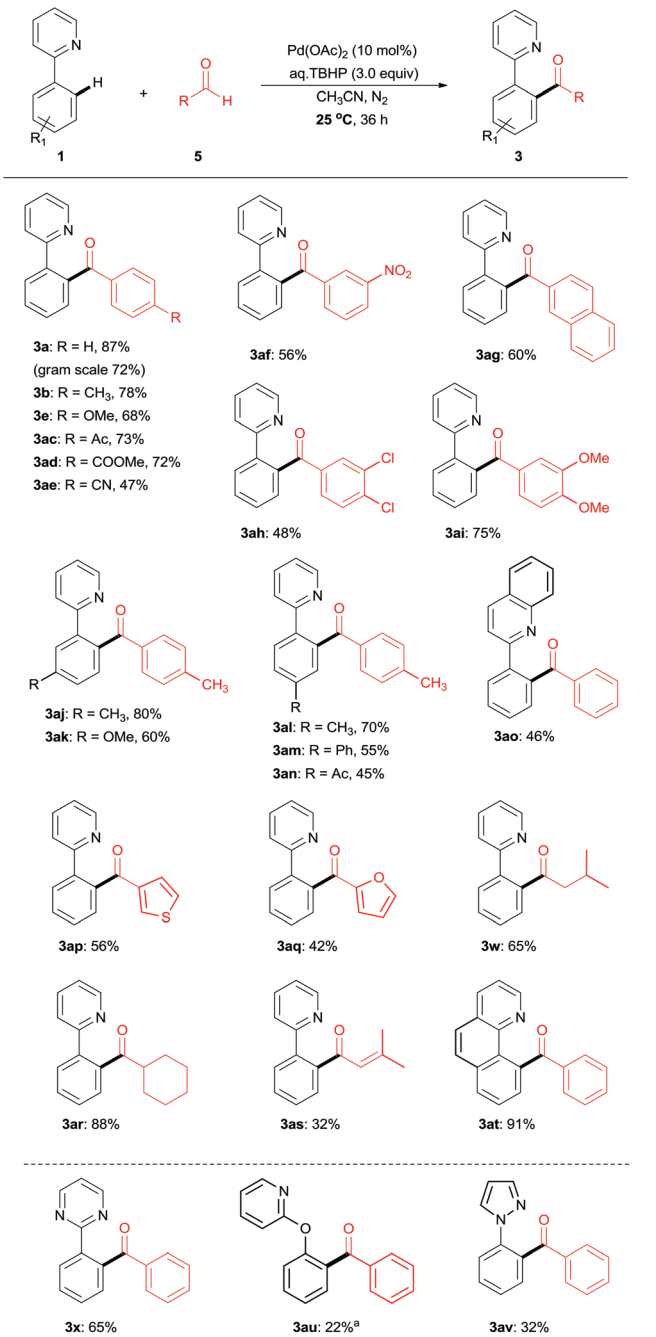
 




**Scheme 3** Substrate scope of 2-phenylpyridines and 2-oxo-2-phenylacetaldehydes. The reaction was carried out on a 0.2 mmol scale, using **1** (1.0 equiv.) and **4** (1.5 equiv.). The yield referred to here is the average isolated yield of at least two experiments.

decarbonylative cross-coupling for arylation has been explored,[24] decarbonylative C–H acylation is not known. We hypothesized that glyoxals can be utilized in palladium-catalyzed decarbonylative C–H acylation reaction. To test, a mixture of 2-phenylpyridine (**1a**) and phenylglyoxal (**4a**) was subjected under the optimized reaction conditions of decarboxylative acylation. Gratifyingly, the corresponding acylation product was isolated in 70% yield (**3a**, Scheme 3). However, the reaction under oxygen did not furnish any acylation product although dioxygen-mediated generation of an alkyl radical from the corresponding aldehydes is known at elevated temperature.[25] Other oxidants such as aq. TBHP or TBHP in decane and even $(NH_4)_2S_2O_8$ were ineffective for this transformation. Surprisingly, a trace amount of the acylation product was isolated in other solvents like DMSO, DMF, DCE and toluene. Therefore, we proceeded to examine the substrate scope under these conditions. To our delight, a number of 2-phenylpyridines as well as phenylglyoxals with different substituents provided the corresponding acylated products with moderate to good yields (Scheme 3). It is noteworthy that halogenated and *ortho*-substituted 2-phynylpyridines also provided a moderate yield of the acylation products which were ineffective under a decarboxylative acylation protocol.

Next we turned our attention to achieve acylation reaction with commercially available and inexpensive aldehydes as acylation agents. From the literature, palladium-catalyzed C–H acylation of 2-phenylpyridine with aryl and alkyl aldehydes is known at high temperature.[26] However, aldehydes are converted into the corresponding acids by oxygen rapidly at high temperature and the yield is decreased.[26b,27] In addition, the oxidant TBHP is explosive at high temperature particularly at the industrial-scale.[28] Keeping this in mind we intended to develop an acylation reaction with aldehydes at room temperature. Our initial trial reaction between 2-phenylpyridine (**1a**) and benzaldehyde (**5a**) under the previous optimized reaction conditions afforded the acylated product in 35% yield (**3a**, Scheme 4). Considering the unique ability of *tert*-butylhydroperoxide (TBHP) to generate the acyl radical from aldehydes,[29]



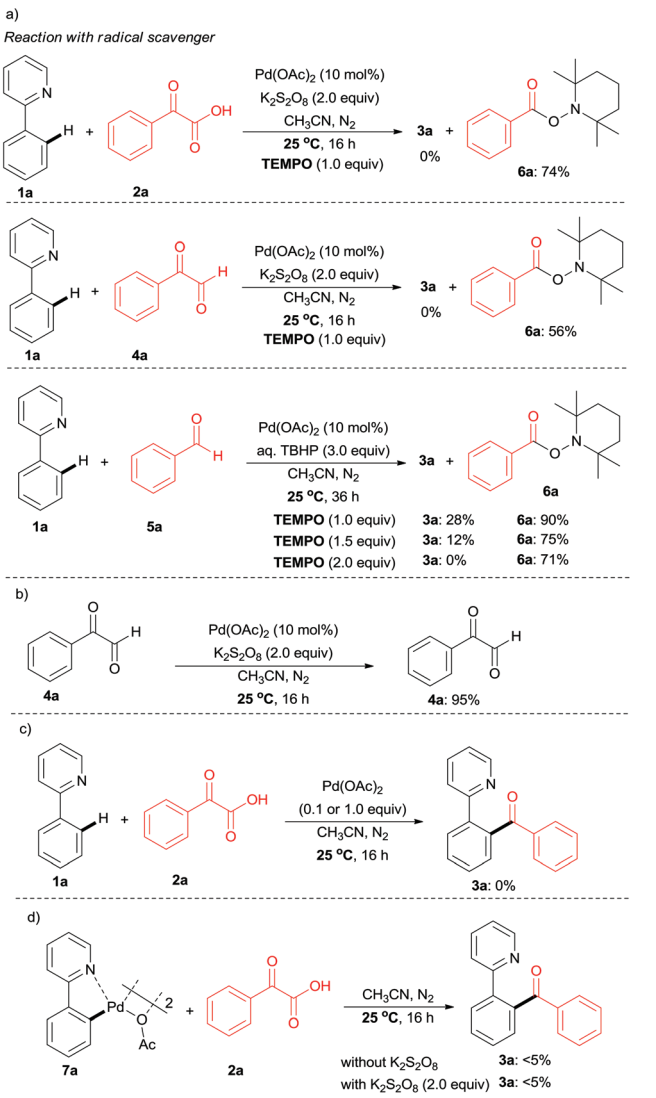

**Scheme 4** Substrate scope of 2-phenylpyridines and aldehydes. The reaction was carried out on a 0.2 mmol scale, using **1** (1.0 equiv.) and **5** (1.5 equiv.). The yield referred to here is the average isolated yield of at least two experiments. [a] The reaction was run for 72 h.

we decided to use TBHP as the oxidant *in lieu* of $K_2S_2O_8$. Surprisingly, the yield was improved to 55% with inexpensive aq. TBHP. Finally an excellent yield of the acylated product (**3a**) in 87% was isolated after stirring the reaction mixture for 36 h at room temperature with the combination of 10 mol% $Pd(OAc)_2$ and 3.0 equiv. of aq. TBHP from 1.0 equiv. of 2-phenylpyridine (**1a**) and 1.5 equiv. of benzaldehyde (**5a**). However, 30% aq. $H_2O_2$ *in lieu* of aq. TBHP did not furnish any acylation product. Of note, the reaction in air or under oxygen provided lower (37%) or no yield and thus the reaction vessel was purged with nitrogen. The reaction under neat conditions also furnished an inferior result (38%).

Subsequently, we explored the substrate scope under the optimized reaction conditions. A wide variety of functional groups on 2-phenylpyridine as well as on aldehydes were found to be compatible under this mild reaction protocol. Besides methoxy, alkyl and aryl groups, halogens such as chloro (**3ah**, Scheme 4), ester (**3ad**, Scheme 4), cyano (**3ae**, Scheme 4), and nitro (**3af**, Scheme 4) remain intact which are useful for further organic transformation. Interestingly, the acyl group on the aldehyde (**3ac**, Scheme 4) is well-tolerated under the reaction conditions which demonstrate the mild nature of the conditions. Interestingly, the aldehyde with a naphthyl moiety furnished the desired product in good yields (**3ag**, Scheme 4). The electron deficient group like acyl on 2-phenylpyridine afforded the moderate yield (**3an**, Scheme 4) which was inferior in the decarboxylative acylation reaction. The reaction with 2-phenylquinoline afforded the acylation product in moderate yield (**3ao**, Scheme 4). Interestingly, the heterocyclic aldehydes, such as furan-2-carbaldehyde and thiophene-3-carbaldehyde provided moderate yields of the desired products (**3ap–3aq**, Scheme 4). In addition, aliphatic aldehydes also afforded the acylation product in moderate to excellent yields (**3w–3as**, Scheme 4). It is important to note that, benzo[*h*]quinoline worked extremely well under the reaction conditions to give the corresponding acylation product in excellent yield (**3at**, Scheme 4). Although, 2-phenoxypyridine, 1-phenyl-1*H*-pyrazole provided a lower yield and the unreacted starting material was recovered (**3au–3av**, Scheme 4) 2-phenylpyrimidine furnished good yield (**3x**, Scheme 4) of the mono-acylation product. Finally, the reaction was reproduced on the gram-scale providing a comparable yield (**3a**, Scheme 4). Other *in situ* convertible acylating agents such as benzyl alcohol, benzyl amine, styrene and toluene did not furnish any acylated product with 2-phenylpyridine under the reaction conditions.

## Investigation of the reaction mechanism

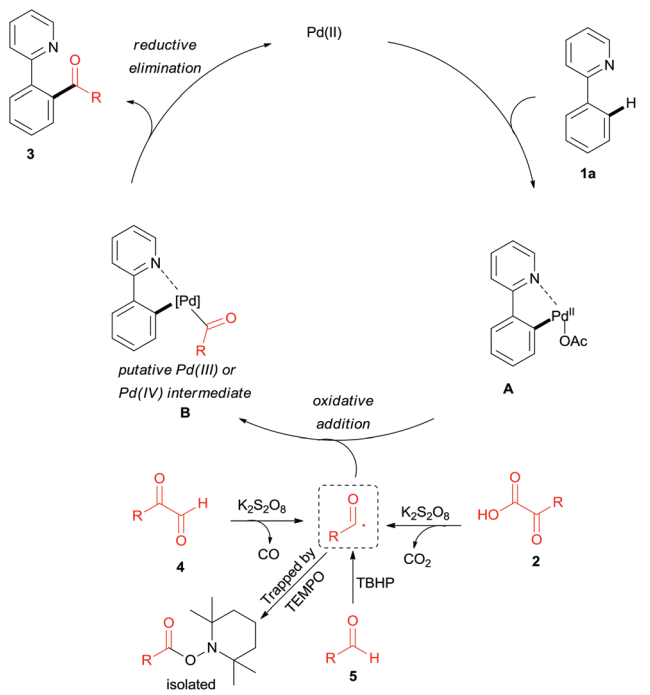
To gain insight into the reaction mechanism, we performed several control experiments. To check whether decarboxylative acylation reaction with phenylglyoxylic acid proceeds through a radical or anionic pathway, radical scavenger 2,2,6,6-tetramethylpiperidinyl-1-oxy (TEMPO) experiment was performed. It was observed that the acylation reaction was completely suppressed with 1.0 equiv. of TEMPO. The TEMPO-acyl adduct, 2,2,6,6-tetramethylpiperidin-1-yl benzoate (**6a**), was detected in electrospray ionization (ESI) mass spectrometry of the crude reaction mixture. Furthermore, it was isolated in 74% yield and well-characterized by NMR and HRMS spectroscopy (Scheme 5a) (see the ESI†). Thus the decarboxylative acylation reaction may proceed through the radical pathway and the acyl radical may generate from the corresponding phenylglyoxylic acids with $K_2S_2O_8$ at room temperature. Similarly, acylation reaction with phenylglyoxal was also completely suppressed with 1.0 equiv. of TEMPO and the TEMPO-acyl adduct (**6a**) was isolated in 56% yield (Scheme 5a). In addition, phenylglyoxal did not oxidize to the phenylglyoxylic acid under the reaction conditions and remained intact (Scheme 5b). Therefore, the possibility of oxidation to the corresponding acid followed by decarboxylative acylation was ruled out and rather an acyl radical may generate in the course of the reaction through decarbonylation of the arylglyoxal. Finally, dehydrogenative




**Scheme 5** Control experiments.

acylation reaction with benzaldehyde was also suppressed substantially with 1.0 and 1.5 equiv. of TEMPO and completely suppressed with 2.0 equiv. of TEMPO. The TEMPO-acyl adduct (**6a**) was also isolated in 71% yield for further confirmation (Scheme 5a). Thus, dehydrogenative acylation may also proceed through the radical pathway and the acyl radical intermediate may form from the corresponding benzaldehyde *via* TBHP oxidation. In the absence of $K_2S_2O_8$ no decarboxylative acylation product was isolated with 10 mol% or even with 1.0 equiv. of $Pd(OAc)_2$ indicating that the combination of palladium and $K_2S_2O_8$ is essential for the reaction to occur (Scheme 5c). Since palladium(II) acetate is known to form a dimeric complex with 2-phenylpyridine through C–H insertion,[30] a palladium dimer complex (**7a**) was prepared separately and subjected to the reaction conditions (Scheme 5d). Only a trace amount of the product was detected suggesting that dimeric palladium species with 2-phenylpyridine may not form under the present reaction conditions whereas a monomeric palladium species may be involved.

From the control experiments and previous reported literature,[29,31,32] we propose the reaction mechanism which is shown in Scheme 6. The pyridine-assisted cyclopalladation with Pd(II) *via* electrophilic palladation may generate the 5-membered palladacycle intermediate **A** (Scheme 6), which undergoes oxidative addition with the acyl radical to yield cyclopalladated Pd(III) intermediate **B** (Scheme 6). Under visible light photoredox and palladium dual catalysis conditions this putative Pd(III) is further oxidized to Pd(IV) with a photoredox catalyst and/or an oxidant.[8f,14b,32c,d,33] However in these catalytic systems, the role of $K_2S_2O_8$ or TBHP in Pd(III)/Pd(IV) oxidation is not clear at this moment and warrants further investigation. The desired acylation product **3** may form through the facile reductive elimination of the intermediate **B** (Scheme 6) and the generation of the Pd(II) catalyst for subsequent runs.




Scheme 6 Plausible mechanism of C($sp^2$)–H acylation.

## Conclusions

In conclusion, we have developed a mild reaction protocol for Pd(II)-catalyzed C($sp^2$)–H acylation using α-ketocarboxylic acids, phenylglyoxals and commercially available, inexpensive aldehydes *via* decarboxylative, decarbonylative and dehydrogenative manifolds respectively. The major advantages of the present protocol are – (a) the reaction operates under mild conditions at room temperature; (b) it does not require a stoichiometric amount of toxic silver(I) salt for decarboxylation of the α-ketocarboxylic acid or as the oxidant; (c) acetonitrile was optimal for the acylation; (d) gaseous $CO_2$, CO or water is formed as by-products avoiding rigorous separation techniques; and (e) the present acylation reaction proceeds through the radical pathway to provide a monoacylation product at the *ortho* position selectively. This room temperature acylation reaction is scalable, energy efficient and avoids the accidental hazard due to explosion of peroxides at elevated temperature. Thus, we anticipate that this mild C–H acylation protocol will find its place in industrial application.

## Experimental section

### General information

Melting points were determined in open end-capillary tubes and are uncorrected. TLC was performed on silica gel plates (silica gel 60, f254), and the spots were visualized with UV light (254 and 365 nm) and $KMnO_4$ stain. $^1H$ and $^{13}C$ NMR spectra were recorded in $CDCl_3$ using TMS as the internal standard. HRMS (*m*/*z*) were recorded using EI (magnetic sector, positive ion) and ESI (Q-TOF, positive ion) techniques. Infrared (IR) spectra were recorded using Fourier transform infrared spectroscopy; only intense peaks were reported.

### General experimental procedure for the decarboxylative acylation reaction between 2-phenylpyridines and α-ketocarboxylic acids, Scheme 2

To an oven-dried 10 mL sealed tube was added a mixture of 2-phenylpyridines (0.2 mmol, 1.0 equiv.), α-ketocarboxylic acids (0.3–0.4 mmol, 1.5–2.0 equiv.), potassium persulfate (108 mg, 0.4 mmol, 2.0 equiv.) and palladium(II) acetate (4.6 mg, 0.02 mmol, 0.1 equiv.) and then dry MeCN (3.0 mL) was added to it. After flushing with nitrogen for 30 seconds, the vessel was immediately sealed with a screw cap. The reaction mixture was allowed to stir for 16 h at room temperature. After that the reaction mixture was quenched with $NaHCO_3$ to remove the unreacted acids. Then the reaction mixture was poured into water (40 mL) and extracted with ethyl acetate

(40 mL). The organic layer was washed with water (10 mL) and brine (10 mL), dried over anhydrous $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography using ethyl acetate/hexane as the eluent to afford the desired product.

Of note, during optimization, it was found that α-ketocarboxylic acids are hygroscopic in nature and thus water or moisture is detrimental to the reaction outcome. Therefore, after flushing with nitrogen the reaction vessel was immediately sealed with a screw cap.

**Phenyl(2-(pyridin-2-yl)phenyl)methanone, 3a, Scheme 2.**[7d] The same general procedure was followed by using 2-phenylpyridine (31.0 mg, 0.2 mmol, 1.0 equiv.), 2-oxo-2-phenylacetic acid (45 mg, 0.3 mmol, 1.5 equiv.), potassium persulfate (108 mg, 0.4 mmol, 2.0 equiv.) and palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv.). Column chromatography ($SiO_2$, eluting with 7 : 3 hexane/ethyl acetate) afforded the desired product as a white solid, (39.5 mg, 76%), mp 105–107 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.36 (d, $J$ = 4.2 Hz, 1H), 7.78 (d, $J$ = 7.8 Hz, 1H), 7.70 (d, $J$ = 7.8 Hz, 2H), 7.61 (t, $J$ = 7.2 Hz, 1H), 7.50–7.56 (m, 4H), 7.39 (t, $J$ = 7.2 Hz, 1H), 7.27 (t, $J$ = 7.2 Hz, 2H), 7.01 (t, $J$ = 4.8 Hz, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 198.2, 156.7, 149.0, 139.6, 139.5, 137.9, 136.3, 132.3, 130.2, 129.4, 129.1, 128.7, 128.5, 128.0, 122.6, 121.9; IR (neat): $\nu_{max}$ 1665, 1587, 1279, 929, 751, 703 cm$^{-1}$; HRMS (EI, $m/z$) calcd for $C_{18}H_{13}NO$ $[M]^+$: 259.0997; found: 259.0979.

**(2-(Pyridin-2-yl)phenyl)(*p*-tolyl)methanone, 3b, Scheme 2.**[7d] The same general procedure was followed by using 2-phenylpyridine (31.0 mg, 0.2 mmol, 1.0 equiv.), 2-oxo-2-(*p*-tolyl)acetic acid (49 mg, 0.3 mmol, 1.5 equiv.), potassium persulfate (108 mg, 0.4 mmol, 2.0 equiv.) and palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv.). Column chromatography ($SiO_2$, eluting with 7 : 3 hexane/ethyl acetate) afforded the desired product as a white solid, (39.0 mg, 72%), mp 97–99 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.41 (d, $J$ = 4.2 Hz, 1H), 7.78 (d, $J$ = 7.2 Hz, 1H), 7.56–7.62 (m, 4H), 7.52 (d, $J$ = 4.2 Hz, 2H), 7.49 (d, $J$ = 8.4 Hz, 1H), 7.09 (d, $J$ = 7.8 Hz, 2H), 7.03–7.06 (m, 1H), 2.33 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 197.9, 156.9, 149.1, 143.1, 139.7, 139.5, 136.2, 135.3, 130.0, 129.7, 128.92, 128.90, 128.8, 128.4, 122.8, 121.9, 21.6; IR (neat): $\nu_{max}$ 1662, 1604, 1433, 1284, 929, 751 cm$^{-1}$; HRMS (ESI, $m/z$) calcd for $C_{19}H_{15}NONa$ $[M + Na]^+$: 296.1051; found: 296.1049.

**(4-(*tert*-Butyl)phenyl)(2-(pyridin-2-yl)phenyl)methanone, 3c, Scheme 2.**[34] The same general procedure was followed by using 2-phenylpyridine (31.0 mg, 0.2 mmol, 1.0 equiv.), 2-(4-(*tert*-butyl)phenyl)-2-oxoacetic acid (62 mg, 0.3 mmol, 1.5 equiv.), potassium persulfate (108 mg, 0.4 mmol, 2.0 equiv.) and palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv.). Column chromatography ($SiO_2$, eluting with 7 : 3 hexane/ethyl acetate) afforded the desired product as a yellowish oil, (46.0 mg, 73%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.40 (d, $J$ = 4.2 Hz, 1H), 7.76 (d, $J$ = 7.8 Hz, 1H), 7.65 (d, $J$ = 8.4 Hz, 2H), 7.46–7.62 (m, 5H), 7.30 (d, $J$ = 8.4 Hz, 2H), 7.00–7.04 (m, 1H), 1.27 (s, 9H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 197.9, 157.0, 156.0, 149.1, 139.7, 139.6, 136.2, 135.1, 130.0, 129.6, 129.0, 128.9, 128.2, 125.0, 122.9, 121.8, 35.0, 31.0; IR (neat): $\nu_{max}$ 2961, 1666, 1598, 1466, 1277, 753 cm$^{-1}$; HRMS (ESI, $m/z$) calcd for $C_{22}H_{21}NONa$ $[M + Na]^+$: 338.1521; found: 338.1523.

**(4-Isobutylphenyl)(2-(pyridin-2-yl)phenyl)methanone, 3d, Scheme 2.** The same general procedure was followed by using 2-phenylpyridine (31.0 mg, 0.2 mmol, 1.0 equiv.), 2-(4-isobutylphenyl)-2-oxoacetic acid (62 mg, 0.3 mmol, 1.5 equiv.), potassium persulfate (108 mg, 0.4 mmol, 2.0 equiv.) and palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv.). Column chromatography ($SiO_2$, eluting with 7 : 3 hexane/ethyl acetate) afforded the desired product as a colourless oil, (45.0 mg, 71%). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.39 (d, $J$ = 4.2 Hz, 1H), 7.76 (d, $J$ = 7.8 Hz, 1H), 7.51–7.62 (m, 6H), 7.45 (d, $J$ = 7.8 Hz, 1H), 7.03 (d, $J$ = 8.4 Hz, 2H), 7.00–7.02 (m, 1H), 2.43 (d, $J$ = 7.2 Hz, 2H), 1.78–1.85 (m, 1H), 0.84 (d, $J$ = 6.6 Hz, 6H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 198.0, 157.0, 149.0, 146.8, 139.7, 139.6, 136.1, 135.5, 130.1, 129.5, 129.1, 128.9, 128.7, 128.4, 123.0, 121.8, 45.3, 30.1, 22.2; IR (neat): $\nu_{max}$ 2957, 1664, 1602, 1281, 930, 751 cm$^{-1}$; HRMS (ESI, $m/z$) calcd for $C_{22}H_{21}NONa$ $[M + Na]^+$: 338.1521; found: 338.1520.

**(4-Methoxyphenyl)(2-(pyridin-2-yl)phenyl)methanone, 3e, Scheme 2.**[7d] The same general procedure was followed by using 2-phenylpyridine (31.0 mg, 0.2 mmol, 1.0 equiv.), 2-(4-methoxyphenyl)-2-oxoacetic acid (54 mg, 0.3 mmol, 1.5 equiv.), potassium persulfate (108 mg, 0.4 mmol, 2.0 equiv.) and palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv.). Column chromatography ($SiO_2$, eluting with 7 : 3 hexane/ethyl acetate) afforded the desired product as a yellowish oil, (35.0 mg, 60%). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.44 (d, $J$ = 4.8 Hz, 1H), 7.78 (d, $J$ = 7.8 Hz, 1H), 7.68–7.70 (m, 2H), 7.56–7.62 (m, 2H), 7.52 (d, $J$ = 4.2 Hz, 2H), 7.48 (d, $J$ = 7.8 Hz, 1H), 7.05–7.07 (m, 1H), 6.76–6.79 (m, 2H), 3.81 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 197.0, 163.0, 157.0, 149.1, 139.6, 139.5, 136.2, 131.9, 130.7, 129.9, 129.0, 128.8, 128.3, 123.0, 121.9, 113.3, 55.3; IR (neat): $\nu_{max}$ 1658, 1597, 1464, 1256, 1027, 753 cm$^{-1}$; HRMS (ESI, $m/z$) calcd for $C_{19}H_{15}NO_2Na$ $[M + Na]^+$: 312.1000; found: 312.0997.

**(2,4-Dimethylphenyl)(2-(pyridin-2-yl)phenyl)methanone, 3m, Scheme 2.** The same general procedure was followed by using 2-phenylpyridine (31.0 mg, 0.2 mmol, 1.0 equiv.), 2-(2,4-dimethylphenyl)-2-oxoacetic acid (53.5 mg, 0.3 mmol, 1.5 equiv.), potassium persulfate (108 mg, 0.4 mmol, 2.0 equiv.) and palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv.). Column chromatography ($SiO_2$, eluting with 7 : 3 hexane/ethyl acetate) afforded the desired product as a light yellow oil, (40.0 mg, 70%). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.46–8.47 (m, 1H), 7.66–7.67 (m, 1H), 7.56–7.60 (m, 3H), 7.49–7.52 (m, 1H), 7.42 (d, $J$ = 7.8 Hz, 1H), 7.11 (d, $J$ = 8.4 Hz, 1H), 7.03–7.05 (m, 1H), 6.92 (s, 1H), 6.76 (d, $J$ = 7.8 Hz, 1H), 2.56 (s, 3H), 2.24 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 199.5, 157.4, 148.7, 141.5, 141.0, 139.8, 139.4, 136.3, 135.2, 132.1, 131.2, 130.3, 129.6, 129.2, 128.4, 125.5, 122.8, 121.8, 21.3, 21.0; IR (neat): $\nu_{max}$ 2924, 1663, 1601, 1436, 1299, 753 cm$^{-1}$; HRMS (EI, $m/z$) calcd for $C_{20}H_{17}NO$ $[M]^+$: 287.1310; found: 287.1305.

**(3,5-Dimethoxyphenyl)(2-(pyridin-2-yl)phenyl)methanone, 3n, Scheme 2.** The same general procedure was followed by using 2-phenylpyridine (31.0 mg, 0.2 mmol, 1.0 equiv.), 2-(3,5-dimethoxyphenyl)-2-oxoacetic acid (63 mg, 0.3 mmol,

1.5 equiv.), potassium persulfate (108 mg, 0.4 mmol, 2.0 equiv.) and palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv.). Column chromatography ($SiO_2$, eluting with 7 : 3 hexane/ethyl acetate) afforded the desired product as a colourless oil, (37.0 mg, 58%). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.40 (d, $J$ = 4.8 Hz, 1H), 7.77 (d, $J$ = 7.8 Hz, 1H), 7.58–7.61 (m, 2H), 7.50–7.54 (m, 3H), 7.04–7.06 (m, 1H), 6.96 (d, $J$ = 1.8 Hz, 2H), 6.50 (t, $J$ = 2.4 Hz, 1H), 3.73 (s, 6H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 197.6, 160.3, 156.7, 149.0, 139.8, 139.5, 139.3, 136.3, 130.2, 129.1, 128.7, 128.4, 122.4, 122.0, 107.3, 105.0, 55.5; IR (neat): $\nu_{max}$ 1670, 1594, 1462, 1302, 1156, 1062, 753 cm$^{-1}$; HRMS (ESI, $m/z$) calcd for $C_{20}H_{17}NO_3Na$ $[M + Na]^+$: 342.1106; found: 342.1007.

**(5-Methoxy-2-(pyridin-2-yl)phenyl)(phenyl)methanone, 3t, Scheme 2.**[26b] The same general procedure was followed by using 2-(4-methoxyphenyl)pyridine (37.0 mg, 0.2 mmol, 1.0 equiv.), 2-oxo-2-phenylacetic acid (60 mg, 0.4 mmol, 2.0 equiv.), potassium persulfate (108 mg, 0.4 mmol, 2.0 equiv.) and palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv.). Column chromatography ($SiO_2$, eluting with 7 : 3 hexane/ethyl acetate) afforded the desired product as a white solid, (46.0 mg, 80%), mp 98–100 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.32 (d, $J$ = 4.8 Hz, 1H), 7.73 (d, $J$ = 8.4 Hz, 1H), 7.70 (d, $J$ = 7.2 Hz, 2H), 7.53 (td, $J$ = 7.8 Hz, 1.2 Hz, 1H), 7.45 (d, $J$ = 7.8 Hz, 1H), 7.38 (t, $J$ = 7.2 Hz, 1H), 7.26–7.28 (m, 2H), 7.14 (dd, $J$ = 8.4 Hz, 2.4 Hz, 1H), 7.06 (d, $J$ = 2.4 Hz, 1H), 6.95–6.97 (m, 1H), 3.89 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 197.9, 159.8, 156.3, 148.8, 140.8, 137.7, 136.2, 132.3, 132.0, 129.9, 129.3, 128.0, 122.0, 121.3, 116.1, 114.0, 55.6; IR (neat): $\nu_{max}$ 1666, 1595, 1462, 1286, 1230, 741, 700 cm$^{-1}$; HRMS (ESI, $m/z$) calcd for $C_{19}H_{15}NO_2Na$ $[M + Na]^+$: 312.1000; found: 312.1003.

**(4-Fluorophenyl)(5-methoxy-2-(pyridin-2-yl)phenyl)methanone, 3u, Scheme 2.** The same general procedure was followed by using 2-(4-methoxyphenyl)pyridine (37.0 mg, 0.2 mmol, 1.0 equiv.), 2-(4-fluorophenyl)-2-oxoacetic acid (67 mg, 0.4 mmol, 2.0 equiv.), potassium persulfate (108 mg, 0.4 mmol, 2.0 equiv.) and palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv.). Column chromatography ($SiO_2$, eluting with 7 : 3 hexane/ethyl acetate) afforded the desired product as a white solid, (39.0 mg, 64%), mp 74–76 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.31 (d, $J$ = 4.8 Hz, 1H), 7.70–7.73 (m, 3H), 7.55 (td, $J$ = 7.8 Hz, 1.8 Hz, 1H), 7.46 (d, $J$ = 7.8 Hz, 1H), 7.14 (dd, $J$ = 8.4 Hz, 2.4 Hz, 1H), 7.4 (d, $J$ = 2.4 Hz, 1H), 6.98 (dd, $J$ = 7.2 Hz, 4.8 Hz, 1H), 6.93 (t, $J$ = 8.4 Hz, 2H), 3.89 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 196.3, 165.1 (d, $J$ = 252.0 Hz), 159.9, 156.1, 148.8, 140.5, 136.3, 134.2 (d, $J$ = 3.0 Hz), 131.8 (d, $J$ = 9.0 Hz), 129.9, 121.9, 121.4, 116.1, 115.1 (d, $J$ = 21.0 Hz), 113.9, 55.6; IR (neat): $\nu_{max}$ 1668, 1596, 1464, 1289, 1230, 850 cm$^{-1}$; HRMS (ESI, $m/z$) calcd for $C_{19}H_{14}FNO_2Na$ $[M + Na]^+$: 330.0906; found: 330.0872.

**(4-Bromophenyl)(5-methoxy-2-(pyridin-2-yl)phenyl)methanone, 3v, Scheme 2.** The same general procedure was followed by using 2-(4-methoxyphenyl)pyridine (37.0 mg, 0.2 mmol, 1.0 equiv.), 2-(4-bromophenyl)-2-oxoacetic acid (92 mg, 0.4 mmol, 2.0 equiv.), potassium persulfate (108 mg, 0.4 mmol, 2.0 equiv.) and palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv.). Column chromatography ($SiO_2$, eluting with 7 : 3 hexane/ethyl acetate) afforded the desired product as a yellowish solid, (49.0 mg, 67%), mp 107–109 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.28 (d, $J$ = 4.8 Hz, 1H), 7.72 (d, $J$ = 8.4 Hz, 1H), 7.55–7.57 (m, 3H), 7.48 (d, $J$ = 7.8 Hz, 1H), 7.39 (d, $J$ = 9.0 Hz, 2H), 7.13 (dd, $J$ = 9.0 Hz, 3.0 Hz, 1H), 7.03 (d, $J$ = 3.0 Hz, 1H), 6.98 (dd, $J$ = 7.2 Hz, 4.8 Hz, 1H), 3.88 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 196.8, 159.9, 155.8, 148.7, 140.3, 136.7, 136.4, 131.7, 131.3, 130.7, 129.8, 127.2, 121.7, 121.5, 116.2, 113.9, 55.6; IR (neat): $\nu_{max}$ 1669, 1586, 1464, 1230, 841, 757 cm$^{-1}$; HRMS (ESI, $m/z$) calcd for $C_{19}H_{14}BrNO_2Na$ $[M + Na]^+$: 390.0106; found: 390.0104.

For the spectroscopy data of compounds **3f**, **3g**, **3h**, **3i**, **3j**, **3k**, **3l**, **3o**, **3p**, **3q**, **3r**, **3s**, **3w** and **3x**, see the ESI.†

## General experimental procedure for the decarbonylative acylation reaction between 2-phenylpyridines and phenylglyoxals, Scheme 3

To an oven-dried 10 mL sealed tube was added a mixture of 2-phenylpyridines (0.2 mmol, 1.0 equiv.), phenylglyoxals (0.3 mmol, 1.5 equiv.), potassium persulfate (108 mg, 0.4 mmol, 2.0 equiv.) and palladium(II) acetate (4.6 mg, 0.02 mmol, 0.1 equiv.) and then dry MeCN (3.0 mL) was added to it. After flushing with nitrogen, the vessel was immediately sealed with a screw cap. The reaction mixture was allowed to stir for 16 h at room temperature. After that the reaction mixture was quenched with $NaHCO_3$. Then the reaction mixture was poured into water (40 mL) and extracted with ethyl acetate (40 mL). The organic layer was washed with water (10 mL) and brine (10 mL), dried over anhydrous $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography using ethyl acetate/hexane as the eluent to afford the desired product.

**(5-Fluoro-2-(pyridin-2-yl)phenyl)(phenyl)methanone, 3y, Scheme 3.**[26b] The same general procedure was followed by using 2-(4-fluorophenyl)pyridine (35.0 mg, 0.2 mmol, 1.0 equiv.), 2-oxo-2-phenylacetaldehyde (40 mg, 0.3 mmol, 1.5 equiv.), potassium persulfate (108 mg, 0.4 mmol, 2.0 equiv.) and palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv.). Column chromatography ($SiO_2$, eluting with 7 : 3 hexane/ethyl acetate) afforded the desired product as a white solid, (26.5 mg, 48%), mp 149–151 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.36 (d, $J$ = 4.8 Hz, 1H), 7.78 (dd, $J$ = 8.4 Hz, 4.8 Hz, 1H), 7.69 (d, $J$ = 7.8 Hz, 2H), 7.58 (td, $J$ = 7.8 Hz, 1.2 Hz, 1H), 7.48 (d, $J$ = 7.8 Hz, 1H), 7.42 (t, $J$ = 7.2 Hz, 1H), 7.25–7.33 (m, 4H), 7.03 (dd, $J$ = 6.6 Hz, 5.4 Hz, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 196.4, 162.6 (d, $J$ = 249.0 Hz), 155.6, 148.9, 141.4 (d, $J$ = 4.5 Hz), 137.2, 136.5, 135.5 (d, $J$ = 1.5 Hz), 132.6, 130.6 (d, $J$ = 7.5 Hz), 129.3, 128.1, 122.4, 122.0, 117.1 (d, $J$ = 21.0 Hz), 116.1 (d, $J$ = 22.5 Hz); IR (neat): $\nu_{max}$ 1661, 1588, 1279, 846, 789 cm$^{-1}$; HRMS (ESI, $m/z$) calcd for $C_{18}H_{12}FNONa$ $[M + Na]^+$: 300.0801; found: 300.0802.

**(5-Chloro-2-(pyridin-2-yl)phenyl)(phenyl)methanone, 3z, Scheme 3.**[15b] The same general procedure was followed by using 2-(4-chlorophenyl)pyridine (38.0 mg, 0.2 mmol, 1.0 equiv.), 2-oxo-2-phenylacetaldehyde (40 mg, 0.3 mmol, 1.5 equiv.),

potassium persulfate (108 mg, 0.4 mmol, 2.0 equiv.) and palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv.). Column chromatography ($SiO_2$, eluting with 7 : 3 hexane/ethyl acetate) afforded the desired product as a white solid, (33.0 mg, 56%), mp 113–115 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.36 (d, $J$ = 4.2 Hz, 1H), 7.74 (d, $J$ = 8.4 Hz, 1H), 7.69 (dd, $J$ = 8.4 Hz, 1.2 Hz, 2H), 7.57–7.61 (m, 2H), 7.52 (d, $J$ = 1.8 Hz, 1H), 7.50 (d, $J$ = 8.4 Hz, 1H), 7.40–7.43 (m, 1H), 7.30 (t, $J$ = 7.8 Hz, 2H), 7.04–7.06 (m, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 195.8, 155.4, 148.9, 141.0, 137.7, 137.2, 136.6, 134.9, 132.6, 130.2, 129.9, 129.3, 129.0, 128.2, 122.4, 122.2; IR (neat): $\nu_{max}$ 1688, 1588, 1458, 1276, 786 cm$^{-1}$; HRMS (ESI, $m/z$) calcd for $C_{18}H_{12}ClNONa$ $[M + Na]^+$: 316.0505; found: 316.0502.

**(5-Bromo-2-(pyridin-2-yl)phenyl)(phenyl)methanone, 3aa, Scheme 3.**[29a] The same general procedure was followed by using 2-(4-bromophenyl)pyridine (47.0 mg, 0.2 mmol, 1.0 equiv.), 2-oxo-2-phenylacetaldehyde (40 mg, 0.3 mmol, 1.5 equiv.), potassium persulfate (108 mg, 0.4 mmol, 2.0 equiv.) and palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv.). Column chromatography ($SiO_2$, eluting with 7 : 3 hexane/ethyl acetate) afforded the desired product as a white solid, (28.5 mg, 42%), mp 109–111 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.36 (d, $J$ = 4.2 Hz, 1H), 7.74 (dd, $J$ = 7.8 Hz, 1.8 Hz, 1H), 7.66–7.69 (m, 4H), 7.59 (td, $J$ = 7.8 Hz, 1.8 Hz, 1H), 7.50 (d, $J$ = 7.8 Hz, 1H), 7.42 (t, $J$ = 7.2 Hz, 1H), 7.30 (t, $J$ = 7.8 Hz, 2H), 7.04 (dd, $J$ = 6.6 Hz, 4.8 Hz, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 196.2, 155.5, 149.0, 141.1, 138.2, 137.2, 136.6, 133.1, 132.6, 131.8, 130.1, 129.4, 128.2, 123.0, 122.4, 122.3; IR (neat): $\nu_{max}$ 1668, 1587, 1458, 1275, 786 cm$^{-1}$; HRMS (ESI, $m/z$) calcd for $C_{18}H_{12}BrNONa$ $[M + Na]^+$: 360.0000, 361.9979; found: 359.9971, 361.9979.

**(3-Methyl-2-(pyridin-2-yl)phenyl)(phenyl)methanone, 3ab, Scheme 3.**[26b] The same general procedure was followed by using 2-(*o*-tolyl)pyridine (34.0 mg, 0.2 mmol, 1.0 equiv.), 2-oxo-2-phenylacetaldehyde (40 mg, 0.3 mmol, 1.5 equiv.), potassium persulfate (108 mg, 0.4 mmol, 2.0 equiv.) and palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv.). Column chromatography ($SiO_2$, eluting with 7 : 3 hexane/ethyl acetate) afforded the desired product as a colourless oil, (27.0 mg, 50%). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.49 (d, $J$ = 4.2 Hz, 1H), 7.65 (d, $J$ = 7.2 Hz, 2H), 7.60 (t, $J$ = 7.2 Hz, 1H), 7.46 (d, $J$ = 7.2 Hz, 1H), 7.40–7.43 (m, 2H), 7.37 (d, $J$ = 7.2 Hz, 1H), 7.28–7.31 (m, 3H), 7.08 (dd, $J$ = 6.6 Hz, 5.4 Hz, 1H), 2.30 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 198.2, 157.3, 148.7, 140.0, 137.6, 136.8, 136.1, 132.6, 132.5, 129.9, 129.8, 128.0, 127.9, 126.2, 125.3, 121.9, 20.1; IR (neat): $\nu_{max}$ 1666, 1589, 1282, 752, 707 cm$^{-1}$; HRMS (ESI, $m/z$) calcd for $C_{19}H_{15}NONa$ $[M + Na]^+$: 296.1051; found: 296.1062.

### General experimental procedure for the dehydrogenative acylation reaction between 2-phenylpyridines and aldehydes, Scheme 4

To an oven-dried 7 mL clear vial was added a mixture of 2-phenylpyridines (0.2 mmol, 1.0 equiv.) and palladium(II) acetate (4.6 mg, 0.02 mmol, 0.1 equiv.) and then dry MeCN (3.0 mL) was added to it. The corresponding aldehydes (0.3 mmol, 1.5 equiv.) were added to the reaction mixture. After flushing with nitrogen for 30 seconds, the vessel was immediately sealed with a screw cap. Then aq. TBHP (82 μL, 0.6 mmol, 3.0 equiv.) was added to the reaction mixture *via* micro-liter syringe. The reaction mixture was allowed to stir for 36 h at room temperature. After completion (as indicated by TLC), the reaction mixture was quenched with $NaHCO_3$. Then the reaction mixture was poured into water (40 mL) and extracted with ethyl acetate (40 mL). The organic layer was washed with water (10 mL) and brine (10 mL), dried over anhydrous $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography using ethyl acetate/hexane as the eluent to afford the desired product.

**Methyl 4-(2-(pyridin-2-yl)benzoyl)benzoate, 3ad, Scheme 4.**[31a] The same general procedure was followed by using 2-phenylpyridine (31.0 mg, 0.2 mmol, 1.0 equiv.), palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv.), methyl 4-formylbenzoate (49 mg, 0.3 mmol, 1.5 equiv.), and aq. *tert*-butyl hydroperoxide (82 μL, 0.6 mmol, 3.0 equiv.). Column chromatography ($SiO_2$, eluting with 7 : 3 hexane/ethyl acetate) afforded the desired product as a white solid, (45.5 mg, 72%), mp 100–102 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.28–8.29 (m, 1H), 7.91 (d, $J$ = 8.4 Hz, 2H), 7.78 (d, $J$ = 7.2 Hz, 1H), 7.71 (d, $J$ = 8.4 Hz, 2H), 7.61–7.64 (m, 1H), 7.54–7.59 (m, 4H), 6.98–7.00 (m, 1H), 3.89 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 197.4, 166.3, 156.1, 148.8, 141.6, 139.4, 139.0, 136.5, 132.8, 130.5, 129.2, 128.9, 128.8, 128.4, 122.2, 122.1, 52.3; IR (neat): $\nu_{max}$ 1717, 1664, 1281, 1107, 743 cm$^{-1}$; HRMS (EI, $m/z$) calcd for $C_{20}H_{15}NO_3$ $[M]^+$: 317.1052; found: 317.1053.

**(3,4-Dichlorophenyl)(2-(pyridin-2-yl)phenyl)methanone, 3ah, Scheme 4.** The same general procedure was followed by using 2-phenylpyridine (31.0 mg, 0.2 mmol, 1.0 equiv.), palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv.), 3,4-dichlorobenzaldehyde (52.5 mg, 0.3 mmol, 1.5 equiv.), and aq. *tert*-butyl hydroperoxide (82 μL, 0.6 mmol, 3.0 equiv.). Column chromatography ($SiO_2$, eluting with 7 : 3 hexane/ethyl acetate) afforded the desired product as a white solid, (31.5 mg, 48%), mp 135–137 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.33 (d, $J$ = 4.2 Hz, 1H), 7.80 (d, $J$ = 7.2 Hz, 1H), 7.78 (d, $J$ = 1.8 Hz, 1H), 7.63–7.66 (m, 2H), 7.59 (d, $J$ = 7.8 Hz, 1H), 7.55 (t, $J$ = 7.2 Hz, 1H), 7.49–7.53 (m, 2H), 7.34 (d, $J$ = 8.4 Hz, 1H), 7.06–7.08 (m, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 195.7, 156.0, 148.8, 139.3, 138.5, 137.8, 136.6, 136.4, 132.5, 130.9, 130.6, 130.1, 129.0, 128.8, 128.4, 128.2, 122.2, 122.1; IR (neat): $\nu_{max}$ 1666, 1580, 1434, 1380, 1275, 955, 747 cm$^{-1}$; HRMS (ESI, $m/z$) calcd for $C_{18}H_{11}Cl_2NONa$ $[M + Na]^+$: 350.0115; found: 350.0117.

**(3,4-Dimethoxyphenyl)(2-(pyridin-2-yl)phenyl)methanone, 3ai, Scheme 4.** The same general procedure was followed by using 2-phenylpyridine (31.0 mg, 0.2 mmol, 1.0 equiv.), palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv.), 3,4-dimethoxybenzaldehyde (50 mg, 0.3 mmol, 1.5 equiv.), and aq. *tert*-butyl hydroperoxide (82 μL, 0.6 mmol, 3.0 equiv.). Column chromatography ($SiO_2$, eluting with 7 : 3 hexane/ethyl acetate) afforded the desired product as a white solid, (48.0 mg, 75%), mp 108–110 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.42–8.43

(m, 1H), 7.77 (d, $J$ = 7.8 Hz, 1H), 7.58–7.60 (m, 1H), 7.56 (td, $J$ = 7.8 Hz, 1.8 Hz, 1H), 7.49–7.52 (m, 2H), 7.46 (d, $J$ = 7.8 Hz, 1H), 7.44 (d, $J$ = 1.8 Hz, 1H), 7.16 (dd, $J$ = 8.4 Hz, 2.4 Hz, 1H), 7.03–7.05 (m, 1H), 6.66 (d, $J$ = 8.4 Hz, 1H), 3.96 (s, 3H), 3.85 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 197.0, 157.0, 152.7, 149.2, 148.6, 139.51, 139.48, 136.2, 130.8, 130.0, 129.0, 128.9, 128.3, 125.2, 122.9, 121.9, 110.9, 109.6, 55.91, 55.89; IR (neat): $\nu_{max}$ 1656, 1588, 1511, 1269, 1128, 753 cm$^{-1}$; HRMS (ESI, $m/z$) calcd for $C_{20}H_{17}NO_3Na$ $[M + Na]^+$: 342.1106; found: 342.1112.

**(4-Methyl-2-(pyridin-2-yl)phenyl)(*p*-tolyl)methanone, 3aj, Scheme 4.** The same general procedure was followed by using 2-(*m*-tolyl)pyridine (34.0 mg, 0.2 mmol, 1.0 equiv.), palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv.), 4-methylbenzaldehyde (36 μL, 0.3 mmol, 1.5 equiv.), and aq. *tert*-butyl hydroperoxide (82 μL, 0.6 mmol, 3.0 equiv.). Column chromatography ($SiO_2$, eluting with 7 : 3 hexane/ethyl acetate) afforded the desired product as a white solid, (46.0 mg, 80%), mp 128–130 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.42 (d, $J$ = 4.2 Hz, 1H), 7.58–7.61 (m, 3H), 7.53 (td, $J$ = 7.8 Hz, 1.8 Hz, 1H), 7.43 (t, $J$ = 7.2 Hz, 2H), 7.32 (d, $J$ = 7.8 Hz, 1H), 7.07 (d, $J$ = 8.4 Hz, 2H), 7.01–7.03 (m, 1H), 2.50 (s, 3H), 2.31 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 198.0, 157.2, 149.1, 143.0, 140.3, 139.8, 136.8, 136.1, 135.4, 129.8, 129.7, 129.2, 129.0, 128.7, 123.1, 121.8, 21.6, 21.4; IR (neat): $\nu_{max}$ 1661, 1605, 1467, 1286, 931, 756 cm$^{-1}$; HRMS (ESI, $m/z$) calcd for $C_{20}H_{17}NONa$ $[M + Na]^+$: 310.1208; found: 310.1217.

**(4-Methoxy-2-(pyridin-2-yl)phenyl)(*p*-tolyl)methanone, 3ak, Scheme 4.** The same general procedure was followed by using 2-(3-methoxyphenyl)pyridine (37.0 mg, 0.2 mmol, 1.0 equiv.), palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv.), 4-methylbenzaldehyde (36 μL, 0.3 mmol, 1.5 equiv.), and aq. *tert*-butyl hydroperoxide (82 μL, 0.6 mmol, 3.0 equiv.). Column chromatography ($SiO_2$, eluting with 7 : 3 hexane/ethyl acetate) afforded the desired product as a colourless oil, (36.5 mg, 60%). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.43–8.44 (m, 1H), 7.58 (d, $J$ = 8.4 Hz, 2H), 7.52–7.55 (m, 2H), 7.39 (d, $J$ = 7.8 Hz, 1H), 7.27 (d, $J$ = 7.8 Hz, 1H), 7.02–7.07 (m, 4H), 3.93 (s, 3H), 2.31 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 197.3, 161.0, 157.2, 149.1, 142.9, 142.1, 136.1, 135.6, 132.0, 131.3, 129.8, 128.7, 123.4, 122.0, 114.6, 113.7, 55.5, 21.5; IR (neat): $\nu_{max}$ 2926, 1659, 1603, 1467, 1284, 1223, 1032, 758 cm$^{-1}$; HRMS (EI, $m/z$) calcd for $C_{20}H_{17}NO_2$ $[M]^+$: 303.1259; found: 303.1256.

**(4-(Pyridin-2-yl)-[1,1′-biphenyl]-3-yl)(*p*-tolyl)methanone, 3am, Scheme 4.** The same general procedure was followed by using 2-([1,1′-biphenyl]-4-yl)pyridine (46.5 mg, 0.2 mmol, 1.0 equiv.), palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv.), 4-methylbenzaldehyde (36 μL, 0.3 mmol, 1.5 equiv.), and aq. *tert*-butyl hydroperoxide (82 μL, 0.6 mmol, 3.0 equiv.). Column chromatography ($SiO_2$, eluting with 7 : 3 hexane/ethyl acetate) afforded the desired product as a white solid, (38.5 mg, 55%), mp 145–147 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.42 (d, $J$ = 4.2 Hz, 1H), 7.88 (d, $J$ = 7.8 Hz, 1H), 7.84 (dd, $J$ = 7.8 Hz, 1.8 Hz, 1H), 7.76 (d, $J$ = 1.8 Hz, 1H), 7.67–7.69 (m, 4H), 7.59 (td, $J$ = 7.8 Hz, 1.8 Hz, 1H), 7.55 (d, $J$ = 7.8 Hz, 1H), 7.47 (t, $J$ = 7.8 Hz, 2H), 7.39 (t, $J$ = 7.2 Hz, 1H), 7.11 (d, $J$ = 7.8 Hz, 2H), 7.04–7.06 (m, 1H), 2.34 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 197.9, 156.5, 149.1, 143.2, 141.2, 140.2, 139.7, 138.3, 136.3, 135.2, 129.8, 129.3, 128.9, 128.8, 128.5, 127.9, 127.5, 127.1, 122.6, 121.9, 21.6; IR (neat): $\nu_{max}$ 1662, 1596, 1462, 1245, 758 cm$^{-1}$; HRMS (ESI, $m/z$) calcd for $C_{25}H_{19}NONa$ $[M + Na]^+$: 372.1364; found: 372.1364.

**1-(3-(4-Methylbenzoyl)-4-(pyridin-2-yl)phenyl)ethanone, 3an, Scheme 4.** The same general procedure was followed by using 1-(4-(pyridin-2-yl)phenyl)ethanone (39.5 mg, 0.2 mmol, 1.0 equiv.), palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv.), 4-methylbenzaldehyde (36 μL, 0.3 mmol, 1.5 equiv.), and aq. *tert*-butyl hydroperoxide (82 μL, 0.6 mmol, 3.0 equiv.). Column chromatography ($SiO_2$, eluting with 7 : 3 hexane/ethyl acetate) afforded the desired product as a white solid, (28.0 mg, 45%), mp 89–91 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.41–8.42 (m, 1H), 8.19 (dd, $J$ = 7.8 Hz, 1.2 Hz, 1H), 8.07 (d, $J$ = 1.8 Hz, 1H), 7.89 (d, $J$ = 8.4 Hz, 1H), 7.59–7.64 (m, 3H), 7.55 (d, $J$ = 7.8 Hz, 1H), 7.08–7.11 (m, 3H), 2.66 (s, 3H), 2.34 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 197.1, 197.0, 155.6, 149.2, 143.6, 143.5, 140.0, 136.6, 136.5, 134.8, 129.6, 129.5, 129.2, 128.9, 122.9, 122.6, 26.8, 21.6; IR (neat): $\nu_{max}$ 2925, 1682, 1599, 1300, 1243, 756 cm$^{-1}$; HRMS (EI, $m/z$) calcd for $C_{21}H_{17}NO_2$ $[M]^+$: 315.1259; found: 315.1248.

**(2-(Pyridin-2-yl)phenyl)(thiophen-3-yl)methanone, 3ap, Scheme 4.** The same general procedure was followed by using 2-phenylpyridine (31.0 mg, 0.2 mmol, 1.0 equiv.), palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv.), thiophene-3-carbaldehyde (26 μL, 0.3 mmol, 1.5 equiv.), and aq. *tert*-butyl hydroperoxide (82 μL, 0.6 mmol, 3.0 equiv.). Column chromatography ($SiO_2$, eluting with 7 : 3 hexane/ethyl acetate) afforded the desired product as a colourless oil, (30.0 mg, 56%). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.46 (d, $J$ = 4.2 Hz, 1H), 7.77 (d, $J$ = 7.2 Hz, 1H), 7.58–7.62 (m, 4H), 7.52 (t, $J$ = 7.2 Hz, 1H), 7.49 (d, $J$ = 7.8 Hz, 1H), 7.42 (d, $J$ = 4.8 Hz, 1H), 7.15–7.16 (m, 1H), 7.07–7.09 (m, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 191.8, 157.0, 149.2, 142.8, 140.0, 139.4, 136.3, 133.9, 130.3, 129.2, 128.7, 128.4, 127.6, 125.8, 122.9, 121.9; IR (neat): $\nu_{max}$ 1656, 1586, 1428, 1273, 858, 752 cm$^{-1}$; HRMS (ESI, $m/z$) calcd for $C_{16}H_{11}NSONa$ $[M + Na]^+$: 288.0459; found: 288.0460.

**3-Methyl-1-(2-(pyridin-2-yl)phenyl)but-2-en-1-one, 3as, Scheme 4.** The same general procedure was followed by using 2-phenylpyridine (31.0 mg, 0.2 mmol, 1.0 equiv.), palladium(II) acetate (4.5 mg, 0.02 mmol, 0.1 equiv.), 3-methylbut-2-enal (29 μL, 0.3 mmol, 1.5 equiv.), and aq. *tert*-butyl hydroperoxide (82 μL, 0.6 mmol, 3.0 equiv.). Column chromatography ($SiO_2$, eluting with 7 : 3 hexane/ethyl acetate) afforded the desired product as a colourless oil, (15.0 mg, 76%). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.64 (d, $J$ = 4.8 Hz, 1H), 7.72 (td, $J$ = 7.8 Hz, 1.8 Hz, 1H), 7.62 (d, $J$ = 7.2 Hz, 1H), 7.58 (d, $J$ = 7.8 Hz, 1H), 7.52–7.54 (m, 1H), 7.46–7.48 (m, 2H), 7.22–7.24 (m, 1H), 6.03 (s, 1H), 2.08 (s, 3H), 1.72 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 196.0, 158.1, 154.8, 149.2, 142.1, 139.4, 136.1, 130.1, 129.5, 128.4, 128.1, 125.3, 123.5, 122.0, 27.5, 20.7; IR (neat): $\nu_{max}$ 2926, 1666, 1615, 1434, 1236, 1012, 752 cm$^{-1}$; HRMS (ESI, $m/z$) calcd for $C_{16}H_{15}NONa$ $[M + Na]^+$: 260.1051; found: 260.1057.

For the spectroscopy data of compounds **3ac**, **3ae**, **3af**, **3ag**, **3al**, **3ao**, **3aq**, **3ar**, **3at**, **3au** and **3av**, see the ESI.†

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# $Cu^{I}/Ag^{I}$-Promoted Decarboxylative Alkynylation of ortho-Nitro Benzoic Acids

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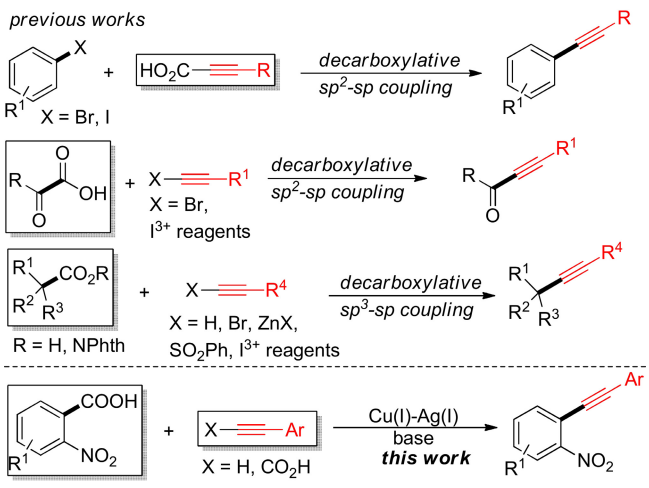
We report herein, a novel copper-silver-promoted alkynylation of *ortho*-nitrobenzoic acids with arylacetylenic acids through a double decarboxylation. The present cross-coupling is extremely challanging due to sluggish decarboxylation of arene carboxylates and deleterious oxidative Glaser-Hay type homocoupling of terminal alkynes. Mechanistically, this $sp^2$-sp cross-coupling may proceed through a silver-assisted decarboxylation of 2-nitrobenzoic acids followed by transmetalation with copper-acetylide and reductive elimination. The *ortho*-nitroacetylenic product is an important precursor for the synthesis of functionalized indoles.

## Introduction

Owing to their unique reactivity as nucleophile as well as electrophile, alkynes are used as one of the most versatile functional groups in organic synthesis and represent an impressive array of utilities in the fuel industry, advanced materials, chemical biology and drug development.[1] However, installation of the alkyne moiety into the organic backbone is heavily dependent on the Sonogashira cross-coupling between vinyl/aryl halides and terminal acetylenes in the presence of palladium/copper(I) bimetallic catalyst.[2] Therefore, development of novel methodology for the synthesis of structurally diverse alkynes is highly desirable. In fact, the direct alkynylation through C–H bonds activation has been investigated in the last decade.[3] But installation of the directing groups to control site-selectivity and their subsequent removal precludes the synthetic fidelity.[4]

As an alternative to conventional cross-coupling or C–H functionalization reactions, decarboxylative cross-coupling has emerged as a modern strategy using readily available and inexpensive; air and moisture stable carboxylic acids as coupling partner.[5] In this case, a mechanistically distinct decarboxylative metalation occurs through the extrusion of $CO_2$. Although decarboxylative biaryl and Heck-type cross-coupling has been well-explored, decarboxylative alkynylation remain underdeveloped.[6] In this vein, three different classes of carboxylic acids have been explored- 1) the propiolic acids undergo decarboxylative metalation to form metal-acetylides for subsequent arylation and heterodiarylation,[7] allylation and benzylation;[8] 2) α-oxocarboxylic acids serve as an excellent acyl radical equivalent which have also been utilized in the decarboxylative ynone synthesis[9] and recently, 3) alkyl carboxylic acids have showcased tremendous potential in decarboxylative alkynylation reactions under radical conditions.[10] To the best of our knowledge, there is no report of decarboxylative $sp^2$-sp cross-coupling using arene carboxylic acids. This might be ascribed due to sluggish decarboxylation of arene carboxylates and deleterious oxidative Glaser-Hay type homocoupling of terminal alkynes. For the first time, we report herein a copper(I)/silver(I)-promoted decarboxylative $sp^2$-sp cross-coupling between 2-nitrobenzoic acid derivatives and alkyne carboxylic acids via *double decarboxylation*. 2-Alkynylated nitroarene product obtained in this protocol is a crucial precursor for the synthesis of a plethora of *N*-heterocycles especially functionalized indoles.[11]




**Scheme 1.** Decarboxylative Alkynylation

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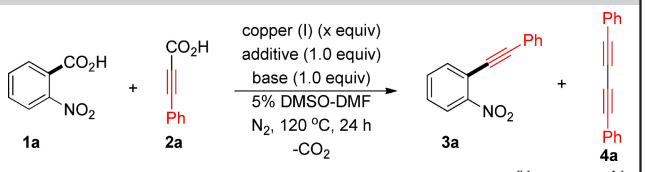
## Results and Discussion

Initially, 2-nitrobenzoic acid (**1a**, Table 1) and phenyl acetylene were chosen as model substrates for the optimization of decarboxylative alkynylation reaction. However, no desired alkynylation product was obtained except oxidative homocoupling of phenyl acetylene with catalytic palladium(0)/copper(I) iodide. We realized that decarboxylative metalation of nitrobenzoic acid is a slower process compared to copper-assisted homocoupling of phenyl acetylene. To circumvent, we chose phenylpropiolic acid (**2a**, Table 1) to induce parity in decarboxylation steps of two cross-coupling partners.[6b,12] Since palladium did not afford the desired product and silver is known to accelerate decarboxylation process, we decided to use silver(I)/copper(I) bimetallic system which was originally developed by the Gooßen's group.[13] Subsequent trials with catalytic copper (I) iodide (20 mol %), in presence of silver(I) carbonate (1.0 equiv) and cesium carbonate (1.0 equiv) afforded decarboxylative protonation of 2-nitrobenzoic acid and 20% of alkyne homocoupling product **4a** (entry 1, Table 1). We hypothesized that sufficient copper-acetylide is essential for the transmetalation with aryl-silver species which is formed through decarboxylation. As expected, increasing the amount of copper(I)iodide to 0.5 and 1.0 equiv. the yield of the desired product was increased to 10% and 28% respectively (entry 2 and 3, Table 1). We examined several ligands such as triphenylphosphine, 1,10-phenanthroline, 2-methylpyridine etc. with catalytic as well as stoichiometric amount of copper(I) catalyst but did not improved the yield further (entry 4, Table 1). Only dtbpy (30%) ligand is provided albeit in low yield (28%) with catalytic amount of copper (30%) (entry 21, Table 1). But unfortunately, after screening several parameters we did not get the improved yield under the catalytic conditions. Other copper catalysts such as copper(I) bromide, copper(I) chloride, copper(II) chlorides, copper(II) acetates etc. also afforded interior results (entry 6,7, 19 Table 1). Among the bases screened, potassium *tert*-butoxide was found to be superior to other bases such as $K_2CO_3$, $NEt_3$, piperidine, pyrrolidine etc. and obtained 40% yield of alkynylation product (**3a**) along with 45% of **4a** (entry 8–11, Table 1). Other solvents such as DMA, DMSO, NMP, $CH_3CN$, etc. provided inferior results (for details see the Supporting Information). Other several additives were also screened but provided lower yield (entry 12–14, Table 1). Interestingly, the yield of desired alkynylation product (**3a**) was increased to 52% using 1.2 equiv. of copper(I) iodide under air (entry 15, Table 1). To accelerate the rate of decarboxylation of 2-nitrobenzoic acid, 2.0 equiv. of silver(I) carbonate was necessary (entry 16, Table 1). Finally heating the reaction mixture at 130 °C for 24 h in a combination of 1.2 equiv. of copper(I) iodide, 2.0 equiv. of silver (I) carbonate and 1.0 equiv. of potassium *tert*-butoxide, the alkynylation product (**3a**) was isolated in 64% yield along with 52% of alkyne homocoupling product (**4a**) (entry 17, Table 1). Interestingly, aerial oxygen was necessary and sufficient for the transformation whereas purging with excess oxygen found to be detrimental (entry 18, Table 1). However, we were unable to suppress alkyne homocoupling product formation even after rigorous screening.

A wide variety of substituents such as alkyl, alkoxyl, chloro on 2-nitrobenzoic acid underwent decarboxylative coupling providing moderate to good yield under the optimized reaction conditions (Table 2). To compare, several reactions were also performed with arylacetylenes to furnish the corresponding alkynylation product (Table 2). Various substituents on phenylacetylene and/or phenylacetylynic acid such as alkyl (**3g**-**3i**, **3m**, **3o**, **3q**, **3r**, Table 2), aryl (**3j**, Table 2), methoxy (**3n**, **3p**, Table 2), chloro (**3k**, **3t**, Table 2), bromo (**3s**, Table 2), fluoro (**3l**, Table 2), trifluoromethoxy (**3u**, Table 2) were well-tolerated under the reaction conditions. The *ortho* substituted phenylpropiolic acids also took part in the reaction providing high to good yield (**3g**, **3o**, **3q**, Table 2). However, other benzoic acids such as *ortho*-methoxybenzoic acid, pentafluorobenzoic acid, *para*-nitrobenzoic acid and heteroaryl carboxylic acids and also alkylated propiolic acids did not furnish any desired product. It was found that the nitro group at *ortho* position of arene carboxylic acids is essential to the desired cross-coupling presumable due the strong inductive effect and coordinating ability of the nitro group that may stabilizes the incipient anion which is formed after decarboxylation. *Ortho* nitrobenzoic acids with another electron-deficient substituent such as 2,4-dinitro-

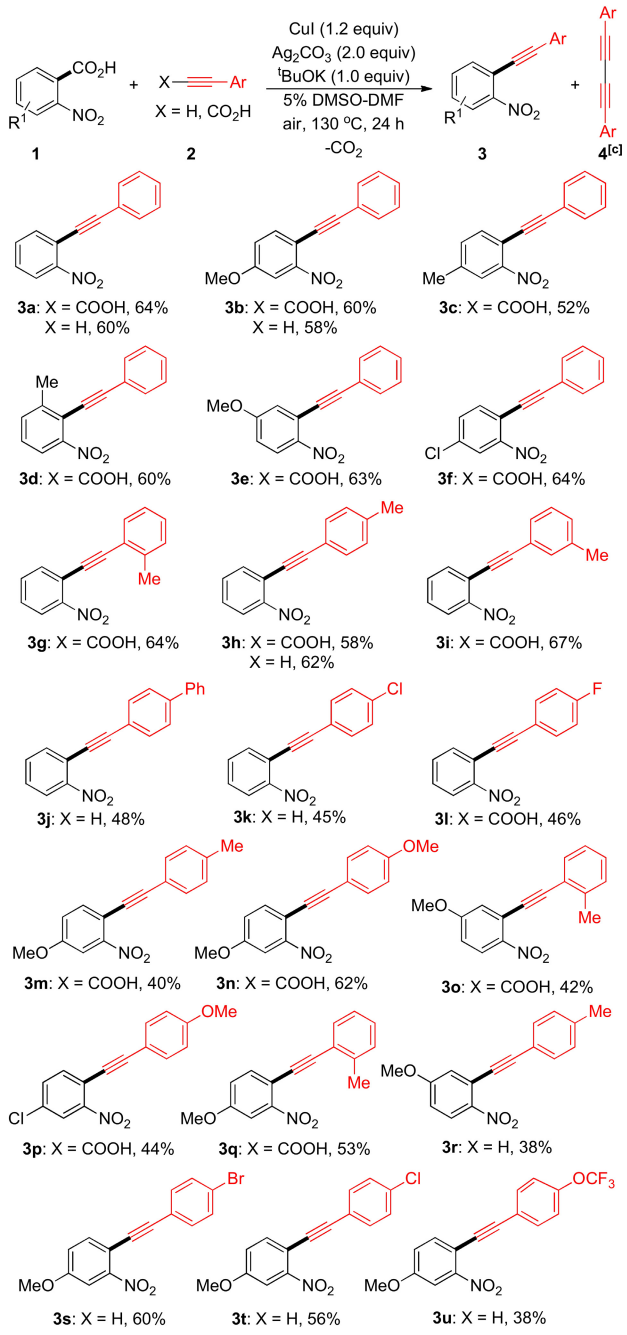
**Table 1.** Optimization of the Reaction Conditions[a]




| entry | Copper (I) | additive | base | yield (%)[b] [**3a**] | **4a**[c] |
|---|---|---|---|---|---|
| 1[d] | CuI (0.2 equiv) | $Ag_2CO_3$ | $Cs_2CO_3$ | 0 | 20 |
| 2 | CuI (0.5 equiv) | $Ag_2CO_3$ | $Cs_2CO_3$ | 10 | 48 |
| 3 | CuI (1.0 equiv) | $Ag_2CO_3$ | $Cs_2CO_3$ | 28 | 42 |
| 4[e] | CuI (1.0 equiv) | $Ag_2CO_3$ | $Cs_2CO_3$ | 0 | 45 |
| 5[f] | CuI (1.0 equiv) | $Ag_2CO_3$ | $Cs_2CO_3$ | nd | 35 |
| 6 | CuCl (1.0 equiv) | $Ag_2CO_3$ | $Cs_2CO_3$ | 20 | 44 |
| 7 | CuBr(1.0 equiv) | $Ag_2CO_3$ | $Cs_2CO_3$ | 18 | 40 |
| 8 | CuI (1.0 equiv) | $Ag_2CO_3$ | $K_2CO_3$ | 20 | 41 |
| 9 | CuI (1.0 equiv) | $Ag_2CO_3$ | pyrrolidine | 30 | 50 |
| 10 | CuI (1.0 equiv) | $Ag_2CO_3$ | $^t$BuOK | 40 | 45 |
| 11 | CuI (1.0 equiv) | $Ag_2CO_3$ | $NEt_3$ | 0 | 52 |
| 12 | CuI (1.0 equiv) | $Ag_2O$ | $^t$BuOK | 27 | 62 |
| 13 | CuI (1.0 equiv) | AgOAc | $^t$BuOK | 5 | 38 |
| 14 | CuI (1.0 equiv) | $K_2S_2O_8$ | $^t$BuOK | 0 | 60 |
| 15[g] | CuI (1.2 equiv) | $Ag_2CO_3$ | $^t$BuOK | 52 | 57 |
| 16[g,h] | CuI (1.2 equiv) | $Ag_2CO_3$ | $^t$BuOK | 60 | 54 |
| **17[g,h,i]** | **CuI (1.2 equiv)** | **$Ag_2CO_3$** | **$^t$BuOK** | **64** | **52** |
| 18[h,i,j] | CuI (1.2 equiv) | $Ag_2CO_3$ | $^t$BuOK | 32 | 55 |
| 19[g,h,i] | $CuCl_2$ (1.2 equiv) | $Ag_2CO_3$ | $^t$BuOK | 30 | 65 |
| 20[g,h,i] | CuI (1.0 equiv) | $Ag_2CO_3$ | - | 0 | 75 |
| 21[g,h,i,k] | CuI (0.3 equiv) | $Ag_2CO_3$ | $^t$BuOK | 28 | 37 |

[a]All reactions were carried out in 0.2 mmol scale using **1a** (1.0 equiv) and **2a** (2.5 equiv). [b]Yields refer to here are isolated yields. [c]% of yield for **4a** based on total amount of **2a** was taken. [d]1.5 equiv. of **2a** was used. [e]1.0 equiv. of $PPh_3$ or 1,10-phenanthroline ligand or 2-methylpyridine was used. [f]0.2 equiv. of $Ag_2CO_3$ was used. [g]Reaction was run under air. [h]2.0 equiv. of $Ag_2CO_3$ was used. [i]The reaction was heated at 130 °C. [j]Reaction was run under $O_2$. [k]30% dtbpy ligand was used.

**Table 2.** Substrate Scope of Decarboxylative Alkynylation[a],[b]

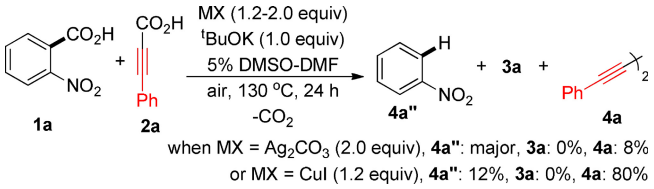



[a]All reactions were carried out in 0.2 mmol scale using **1** (1.0 equiv) and **2** (2.5 equiv).[b]Yields refer to the average of isolated yields of at least two experiments.[c]In every cases 40–50% yield of **4** was separated with respect to total amount of **2** was taken.

the formation of 2-phenylindole from **3a** (see the Supporting Information).

## Reaction Mechanism

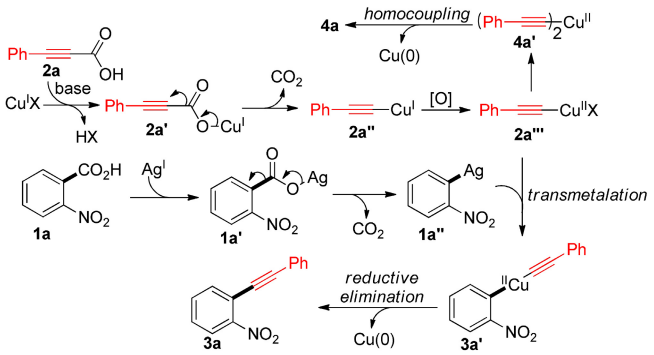
Next, we performed few control experiments to gain insight of the reaction mechanism. The standard reaction without copper salt did not furnish any desired alkynylation product (**3a**) instead nitrobenzene (**4a"**) was formed predominantly through decarboxylative protonation and a trace amount of alkyne homocoupling product (**4a**) (Scheme 2). Furthermore, in the




**Scheme 2.** Control Experiments

absence of silver salt alkyne homocoupling product (**4a**) was favored (80%) along with the formation of nitrobenzene (**4a"**) (12%) (Scheme 2). Therefore, copper is involved in the formation of copper-acetylide via decarboxylation of propiolic acids and silver is participating in the formation of aryl-Ag species via decarboxylation of the nitrobenzoic acids.

Based on these control experiments and previous literature on copper/silver bimetallic system,[13] it is speculated that initially a silver carboxylate forms followed by aryl-silver species, **1a"** (Scheme 3) through the extrusion of $CO_2$. On the other




**Scheme 3.** Plausible Mechanism

benzoic acid resulted in decarboxylative protonation product only. This indicates that electron withdrawing substituents may facilitate the decarboxylation but they decrease the ability of the aryl anion to serve as a σ-donor for the copper(II)-acetylide. The same observation was also found in our previous work of decarboxylative allylation of *ortho* nitrobenzoic esters.[14] Selective reduction of nitro group followed by cyclization leads to

hand, a copper(I)-acetylide, **2a"** is formed either via decarboxylative metalation of arylpropiolic carboxylate which is form through base mediated deprotonation of arylpropiolic acid or direct deprotonation of the phenylacetylene by base which is converted to copper(II)-acetylide, **2a'''** (Scheme 3) under the oxidative conditions here aerial oxygen or silver may acts as an oxidant. Subsequently, a transmetalation between aryl-silver

and copper(II)-acetylide may leads to the aryl,alkyne-copper intermediate, **3a'** (Scheme 3). There is a possibility of disproportionation to generate copper(III) species for facile reductive elimination at this step and generate a copper(I) species for subsequent runs.[15] However, under the stoichiometric copper salt catalysis direct reductive elimination from the copper(II) intermediate to furnish the alkynylation product is also plausible. However, the exact mechanism is unclear at this moment and warrants further studies.

## Conclusions

In conclusion, we have developed a novel $Cu^{I}/Ag^{I}$-promoted alkynylation of nitroarenes through a double decarboxylation. This present approach of using two decarboxylations in an oxidative alkynylation is an excellent strategy to address challenging alkynylations. The 2-alkynyl nitroarenes serve as an important precursor for the synthesis of a plethora of *N*-heterocycles especially functionalized indoles.

### Supporting Information Summary

The Supporting Information contains optimization details, experimental procedures, all the spectroscopic data, $^{1}H$ and $^{13}C$ NMR spectra for all synthesized compounds.

## *Acknowledgement*

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## *Conflict of Interest*

The authors declare no conflict of interest.

**Keywords:** Alkynylation · Cu–Ag bimetallic · Double decarboxylation · 2-Nitrobenzoic acid · $sp^2$-sp Cross-coupling

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# Carboxyl radical-assisted 1,5-aryl migration through Smiles rearrangement†

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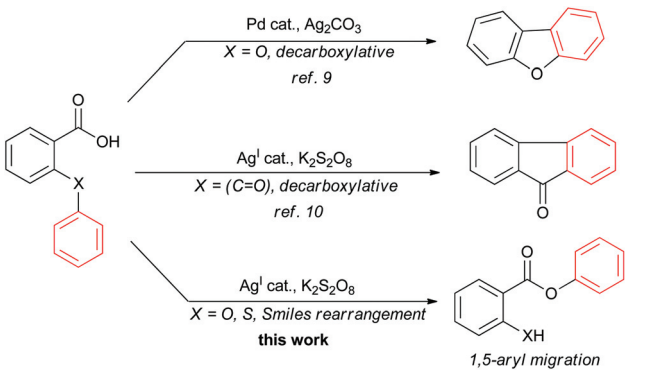
We report herein, a silver(I)-catalyzed Smiles rearrangement of 2-aryloxy- or 2-(arylthio)benzoic acids to provide aryl-2-hydroxybenzoate or aryl-2-mercaptobenzoate dimer, respectively, through 1,5-aryl migration from oxygen or sulfur to carboxylate oxygen. Mechanistically, the aryl ether moiety undergoes an intramolecular *ipso* attack by the carboxyl radical followed by a C–O or C–S bond cleavage. Aryl-2-mercaptobenzoates undergo oxidative dimerization through a thiol moiety *in situ*.

## Introduction

The rearrangement reactions provide concise routes to atom-economic synthesis in organic chemistry.[1] In this vein, the Smiles rearrangement offers a unique opportunity to the synthesis of privileged medicinal scaffolds originally through an intramolecular nucleophilic aromatic substitution.[2] Varieties of Smiles rearrangement such as Truce–Smiles,[3] Ugi–Smiles[4] have been explored for multicomponent reactions (MCR) in medicinal chemistry. However, the potential of radical-Smiles rearrangement has been realized recently.[5] Notably, the Zard group explored a peroxide-mediated radical-Smiles rearrangement to access aryl- or pyridylacetic acid derivatives from *N*-(α-xanthyl)acetanilides or *N*-(α-xanthyl)acetylaminopyridines, respectively.[6] Recently, a photoredox-catalyzed synthesis of a difluoro-substituted spirocyclic ORL-1 antagonist through radical-Smiles rearrangement was reported by the Stephenson group which provides an alternative and practical route with easily available starting materials at industrially relevant scale and catalyst loading.[7]

Carboxylic acids have been explored as inexpensive, readily available, air- and moisture-stable cross-coupling partners.[8] The Glorius group reported a palladium-catalyzed decarboxylative intramolecular C–H arylation to afford dibenzofuran using 2-aryloxybenzoic acids.[9] Alternatively, silver(I)-catalyzed decarboxylative Pschorr-type cyclization to afford fluorenone was reported by the Greaney group.[10] The Baran group also employed this $Ag(I)/K_2S_2O_8$ catalytic system for the generation of aryl radicals from a boronate counterpart which has been trapped intra- and intermolecularly.[11] Recently, a similar catalytic system has been utilized for the decarboxylative Minisci-type arylation with benzoic acid derivatives.[12] Intrigued by these earlier reports we were interested to develop a silver-catalyzed decarboxylative dibenzofuran synthesis from 2-aryloxybenzoic acids in an intramolecular fashion. Interestingly, we observed 1,5-aryl migration through Smile-type rearrangement *in lieu* of the expected decarboxylative dibenzofuran formation (Scheme 1). Since radical aryl migration is a useful tool in organic synthesis,[13] we were interested to develop this rearrangement reaction. From literature, a persulfate-mediated uncontrolled 1,5-aryl migration/oxidative dimerization cascade in water was reported.[14] Surprisingly, in our present study, the 1,5-aryl migratory product formed predominantly and a trace amount (<5%) of dimerization product was observed in electrospray ionization (ESI) mass spectrometry of the crude reaction mixture (see the ESI†). A copper-catalyzed domino aryl




**Scheme 1** Divergent syntheses from *ortho*-substituted benzoic acids.

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† Electronic supplementary information (ESI) available: Starting materials preparation, control experiments, optimization details, $^1H$, $^{13}C$ NMR spectra for all synthesized compounds, and crystallographic data of **2t**. CCDC 1498919. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6ob01758d

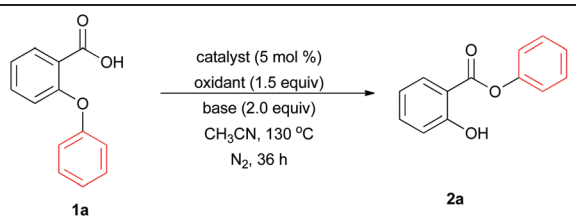
migration/C–O/C–N bond formation for the synthesis of dibenzoxazepinones,[15] and a base-promoted 1,5-aryl migration through Smiles rearrangement were reported.[16] However, the latter protocol is limited to the nicotinamides only where the phenolic hydroxyl group is stabilized by the *ortho* pyridinyl nitrogen. We report herein, a silver(I)-catalyzed 1,5-aryl migration of 2-aryloxybenzoic acids *via* C–O/C–S bond cleavage and C–O bond formation cascade. The corresponding thioethers provided the rearranged product with disulfide bond formation under this oxidative condition.

## Results and discussion

To optimize the reaction conditions, 2-phenoxybenzoic acid was chosen as a model substrate. Initially, a catalytic amount of silver(I) nitrate in the presence of 3.0 equiv. of $K_2S_2O_8$ afforded the Smiles rearrangement product in 34% yield. Decreasing the amount of oxidant to 1.5 equiv., the yield was further improved. However, other common oxidants such as aq. *tert*-butyl hydroperoxide, (diacetoxyiodo)benzene (PIDA), benzoyl peroxide or even ammonium persulfate were not effective for this transformation. Similarly, other silver salts, palladium(II) triflate, tris(acetylacetonato)iron(III) , nickel(II) triflate, copper(II) acetate and tetrabutylammonium iodide were proved to be inferior catalysts compared to silver(I) nitrate. Gratifyingly, the yield was improved with the addition of sodium trifluoroacetate as a base. After screening several bases, ultimately potassium trifluoroacetate provided the migratory product in good yields (for details see the ESI†). Acetonitrile was the solvent of choice since other solvents such as dichloroethane, *N*,*N*-dimethylformamide, toluene *etc*. afforded no or inferior yields. A substantial amount of decomposition product formation was observed which we could not eliminate even after rigorous optimization. Interestingly, salicylic acid formation through hydrolysis of the Smiles rearrangement product was not observed under the reaction condition.

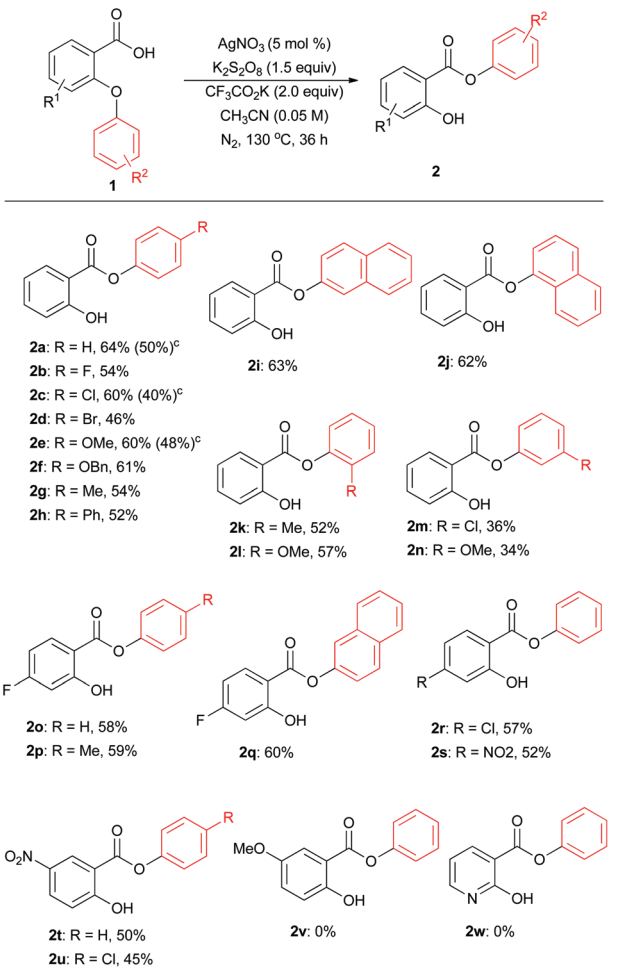
Next we explored the substrate scope under the optimized reaction conditions. The starting materials were synthesized through a copper-catalyzed cross-coupling of 2-halobenzoic acid and phenol or thiophenol derivatives. A wide range of substrates underwent Smiles rearrangement to provide 1,5-aryl migratory products. Several substituents on the phenol component such as alkyl (**2g**, **2k**, **2p**, Scheme 2), aryl (**2h**, Scheme 2), alkoxyl (**2e**, **2f**, **2l**, **2n**, Scheme 2), chloro (**2c**, **2m**, **2u**, Scheme 2), bromo (**2d**, Scheme 2) and fluoro (**2b**, Scheme 2), were well tolerated under the reaction conditions.

**Table 1** Optimization of the reaction conditions[a,b]




| Entry | Catalyst (5 mol%) | Oxidant (1.5 equiv.) | Base (2.0 equiv.) | Yield[b] (%) |
|---|---|---|---|---|
| 1[c] | $AgNO_3$ | $K_2S_2O_8$ | — | 34 |
| 2 | $AgNO_3$ | $K_2S_2O_8$ | — | 44 |
| 3 | $AgNO_3$ | aq. TBHP | — | 0 |
| 4 | $AgNO_3$ | $(NH_4)_2S_2O_8$ | — | 27 |
| 5 | $AgNO_3$ | $PhI(OAc)_2$ | — | 0 |
| 6 | $AgNO_3$ | $(PhCOO)_2$ | — | Trace |
| 7 | AgOAc | $K_2S_2O_8$ | — | 34 |
| 8 | $Ag_2CO_3$ | $K_2S_2O_8$ | — | 36 |
| 9 | $Pd(TFA)_2$ | $K_2S_2O_8$ | — | Trace |
| 10 | $Fe(acac)_3$ | $K_2S_2O_8$ | — | 36 |
| 11 | $Ni(OTf)_2$ | $K_2S_2O_8$ | — | 35 |
| 12 | $Cu(OAc)_2$ | $K_2S_2O_8$ | — | 25 |
| 13 | TBAI | $K_2S_2O_8$ | — | 30 |
| 14 | $AgNO_3$ | $K_2S_2O_8$ | $CF_3CO_2Na$ | 50 |
| **15** | **$AgNO_3$** | **$K_2S_2O_8$** | **$CF_3CO_2K$** | **64** |
| 16 | — | $K_2S_2O_8$ | $CF_3CO_2K$ | 37 |
| 17 | $AgNO_3$ | — | $CF_3CO_2K$ | 0 |

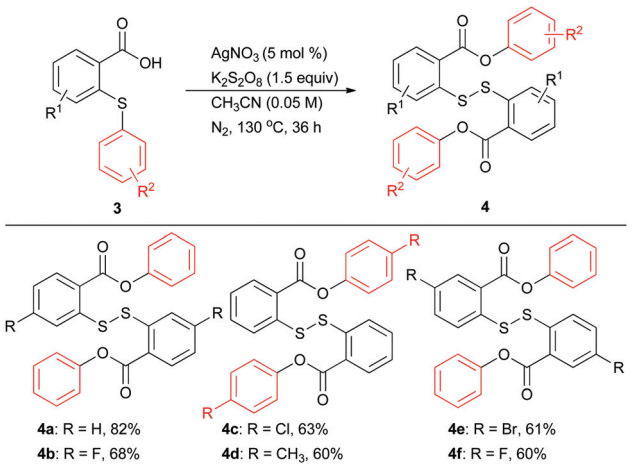
[a] All reactions were carried out in 0.1 mmol scale. [b] Yields refer to here are overall isolated yields. [c] 3.0 equiv. of $K_2S_2O_8$ was used.




**Scheme 2** Substrate scope with diaryl ethers. The reaction was carried out in 0.1 mmol scale, 0.05 M. The yield referred to here is the average isolated yield of at least two experiments. [a] The reaction was performed in 0.5 mmol scale.

Interestingly, substrates derived from 1- and 2-naphthols (**2i**, **2j**, **2q**, Scheme 2) also furnished the migratory products in good yields. Similarly, substitutions on the benzoic acid moiety such as fluoro (**2o–2q**, Scheme 2), chloro (**2r**, Scheme 2), and nitro groups (**2s–2u**, Scheme 2) were also tolerated. A representative structure of the migratory product has been unambiguously characterized by X-ray crystallography (**2t**). An electron-rich benzoic acid such as 5-methoxy-2-phenoxybenzoic acid, **1v** was unreactive under the reaction condition, however, it was difficult to predict the influence of the electronic nature of the substituents since a substantial amount of decomposition products were observed. Unfortunately, the yield of the products was decreased to some extent at higher scale. For example, in a reaction at 0.5 mmol scale, **1a** provided 50% yield of the desired product **2a** (Scheme 2). Similarly, **2c** and **2e** were isolated in 40 and 48% yields respectively at 0.5 mmol scale. Phenyl ether of nicotinic acid, **1w**, did not provide any desired product. Interestingly, the corresponding benzamide in place of benzoic acid did not afford any desired product which indicates a distinct reaction mechanism to the base-promoted anionic Smiles rearrangement.[16] The desired product was hydrolyzed to provide the corresponding salicylic acid (**6a**) and phenol in an alcoholic sodium hydroxide solution (see the ESI†).

On the accomplishment of Smiles rearrangement of 2-aryloxybenzoic acids, we were interested to examine the migratory event of the corresponding thioethers. Under the optimized conditions, the corresponding migratory product (**4a**) with disulfide bond was isolated albeit in moderate yield and a substantial amount of starting material was recovered. Gratifyingly, excellent to good yield of the corresponding Smiles rearrangement product was isolated by simply omitting the base from the standard reaction conditions. From $^1$H NMR and mass spectroscopy it was also confirmed that the free thiol groups underwent oxidative homocoupling to furnish the disulfide linkage *in situ*. This rearranged disulfide product was also observed as a byproduct (15%) in the persulfate mediated oxidation of diphenyl sulfide-2-carboxylic acids.[17] Gratifyingly, under our optimized conditions, a number of 2-arylmarcapto benzoic acids with different substituents provided the 1,5-aryl migratory products followed by oxidative homocoupling products in good to high yields (Scheme 3). Unfortunately, 5-methoxy-2-(phenylthio)benzoic acid was unreactive under the reaction conditions. The disulfide linkage was easily reduced to the corresponding thiols (**5a**) with triphenylphosphine (see the ESI†).



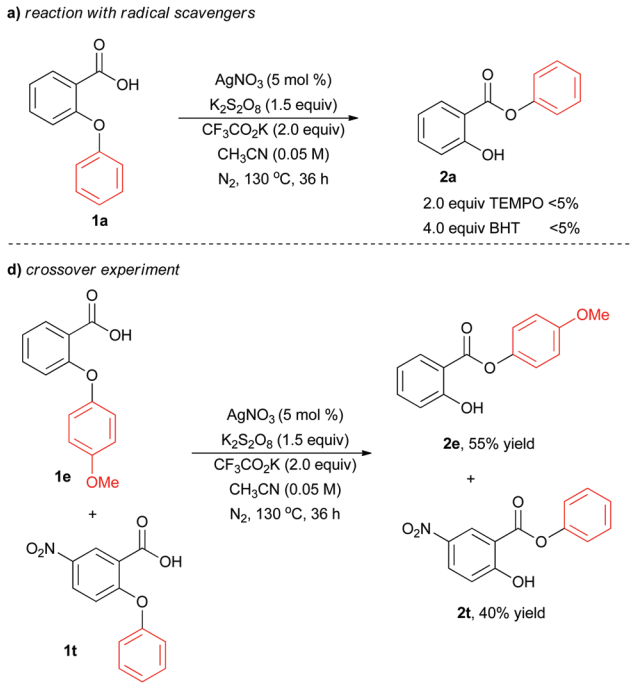

**Scheme 3** Substrate scope with diaryl thioethers. The reaction was carried out in 0.2 mmol scale, 0.05 M. The yield referred to here is the average isolated yield of at least two experiments.

## Investigation of the reaction mechanism

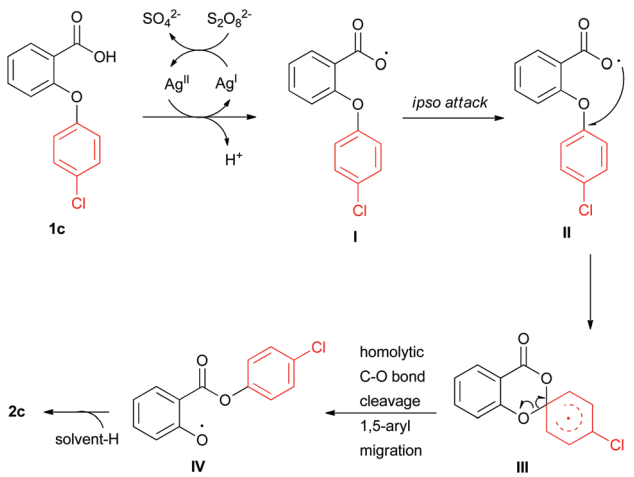
We performed several control experiments to understand the mechanism of this unexpected result. Generation of an aryl radical through the decomposition of aryl diazonium salts and aryl boronates is an energetically favourable process which occurs spontaneously under mild conditions.[11,18] However, generation of an aryl radical through decarboxylation is a high energetic process which occurs at elevated temperature.[12] In the case of 2-aroylbenzoic acid, the incipient radical generated through decarboxylation is stabilized by the *ortho*-ketone group.[10] In contrast, in this present study, the incipient radical is destabilized by the *ortho* ether moiety. This is consistent with our previous observation that *ortho*, *ortho*-dimethoxy carboxylic acid does not decarboxylate with silver(I) catalyst whereas palladium catalyst is effective.[19] Previously, an Ag(I)/$K_2S_2O_8$ catalytic system has been utilized for C–H carboxylation in the biaryl system.[20] However, in this case C–H insertion of the carboxyl radical is not favoured due to the formation of a seven-membered ring. Instead, an *ipso* attack to the ether carbon is favoured and a concomitant homolytic C–O bond cleavage may occur. Typically, reductive cleavage of an inert diaryl ether linkage is possible by nickel catalyst.[21] However, simple diaryl ethers or 2-aryloxybenzamides did not furnish any product under this optimized condition. Therefore, 2-carboxylic acid was found to be crucial for the reaction to occur. The reaction was completely arrested with the addition of radical scavengers such as 2.0 equiv. of 2,2,6,6-tetramethylpiperidinyl-1-oxy (TEMPO) or 4.0 equiv. of butylated hydroxytoluene (BHT) (Scheme 4a). Therefore, the reaction would appear to proceed through a radical mechanism. The involvement of a radical mechanism is further supported by the fact that the reaction also proceeds with persulfate in the absence of silver(I) nitrate to provide the desired product in moderate yield (entry 16, Table 1).[14,17] In order to gain insight further, we performed a cross-over experiment. When an equimolar mixture of **1e** and **1t** was subjected to the reaction conditions no cross-over products were detected in $^1$H NMR as well as ESI mass spectrometry (Scheme 4b) (see the ESI†). This suggests that the reaction may involve an intramolecular rearrangement for 1,5-aryl migration.

From the control experiments and substitution pattern of the observed products, we postulated the reaction mechanism. In the presence of catalytic silver(I) salt and stoichiometric persulfate anion the carboxyl radical **I** (Scheme 5) is generated. Instead of decarboxylation the carboxyl radical then undergoes




Scheme 4 Control experiments.




Scheme 5 Plausible mechanism of 1,5-aryl migration.

an *ipso* attack to the arylether moiety **II** (Scheme 5). A concomitant homolytic C–O bond cleavage occurs which lead to the formation of aryl ester through 1,5 aryl migration **IV** (Scheme 5). The incipient phenoxyl radical may abstract a hydrogen atom from solvent or reaction medium to give the final migratory product **2c** (Scheme 5). This phenomenon is well-established in the previous literature.[14,22] Additionally, the reaction in nitromethane also provides the migratory product **2a** in lower (48%) yield. However, the exact nature of hydrogen, whether it is a proton or hydride, is not clear at this moment. In the case of thioethers, the homocoupling product may occur through thiyl radical dimerization. The dimerization also may occur from the final migratory thiol product under the oxidative reaction conditions. To probe, when monomer of **4a** was subjected to the reaction conditions it furnished the dimerised product **4a** in quantitative yield. However, the possibility of thiyl radical dimerization is also plausible.

## Conclusions

In conclusion, we have developed a silver(I)-catalyzed selective 1,5-aryl migration of 2-aryloxy- or 2-(arylthio)benzoic acids through radical Smiles rearrangement. This unexpected aryl translocation occurs through an intramolecular *ipso* attack of the carboxyl radical to the aryl ether instead of expected intramolecular decarboxylative arylation to afford dibenzofuran. Subsequently, inert C–O bond cleavage of the diaryl ether occurs selectively. The corresponding thioethers also furnished the migratory products with disulfide linkage under this oxidative condition. We anticipate that the present catalytic system could be useful for the selective C–O bond cleavage in biomass conversion.

## Experimental section

### General information

Melting points were determined in open end-capillary tubes and are uncorrected. TLC was performed on silica gel plates (silica gel 60, f254), and the spots were visualized with UV light (254 and 365 nm) and $KMnO_4$ stain. $^1H$ and $^{13}C$ NMR spectra were recorded in $CDCl_3$ using TMS as the internal standard. HRMS (*m*/*z*) were measured using EI (magnetic sector, positive ion) and ESI (Q-TOF, positive ion) techniques. Infrared (IR) spectra were recorded on a Fourier transform infrared spectrometer; only intense peaks were reported.

### General experimental procedure for the preparation of 2-phenoxybenzoic acids, Scheme 2[23]

To an oven-dried 100 mL round bottom flask equipped with magnetic stir bar, 2-halobenzoic acid (6.2 mmol, 1.0 equiv.) was added in 50 mL of dimethylformamide (DMF), followed by phenol (12.4 mmol, 2.0 equiv.), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (2.6 mL, 18.6 mmol, 3.0 equiv.), pyridine (0.1 mL), copper(0) (52 mg, 0.81 mmol), and copper(I) iodide (53 mg, 0.28 mmol). The reaction mixture was heated to 160 °C under nitrogen atmosphere. After consumption of the starting materials as indicated by TLC (typically 2 h) the reaction mixture was cooled and acidified with 3 M HCl until no more precipitate was formed. The resulting precipitates and reaction mixture were extracted with dichloromethane (60 mL) and cold water (70 mL). The organic layer was washed with cold water (20 mL × 3) and brine (10 mL), dried over anhydrous $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography using

ethyl acetate–hexane as eluent to afford the desired white solid product.

**2-Phenoxybenzoic acid, 1a, Scheme 2.**[23] The same general procedure was followed by using 2-iodobenzoic acid (1.55 g, 6.2 mmol, 1.0 equiv.) and phenol (1.20 g, 12.4 mmol, 2.0 equiv.). Column chromatography ($SiO_2$, eluting with 7 : 3 hexane–ethyl acetate) afforded the desired product as a white solid, (1.14 g, 86%), mp 107–109 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 12.84 (br s, 1H), 7.81 (d, $J$ = 7.8 Hz, 1H), 7.54 (td, $J$ = 8.1 Hz, 1.8 Hz, 1H), 7.33 (t, $J$ = 8.4 Hz, 2H), 7.24 (t, $J$ = 7.5 Hz, 1H), 7.06 (t, $J$ = 7.2 Hz, 1H), 6.98 (d, $J$ = 8.1 Hz, 1H), 6.88 (d, $J$ = 8.4 Hz, 2H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 166.6, 157.5, 154.9, 133.5, 131.4, 129.9, 124.6, 124.0, 122.8, 121.0, 117.6.

**2-(4-Fluorophenoxy)benzoic acid, 1b, Scheme 2.**[9] The same general procedure was followed by using 2-iodobenzoic acid (1.55 g, 6.2 mmol, 1.0 equiv.) and 4-fluorophenol (1.40 g, 12.4 mmol, 2.0 equiv.). Column chromatography ($SiO_2$, eluting with 7 : 3 hexane–ethyl acetate) afforded the desired product as a white solid, (1.12 g, 78%), mp 142–144 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 12.91 (br s, 1H), 7.82 (dd, $J$ = 7.8 Hz, 1.8 Hz, 1H), 7.56 (td, $J$ = 8.4 Hz, 1.8 Hz, 1H), 7.15–7.29 (m, 3H), 6.93–7.00 (m, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 166.6, 157.9 (d, $J$ = 237.8 Hz), 155.2, 153.5 (d, $J$ = 2.2 Hz), 133.6, 131.4, 124.3, 124.0, 120.6, 119.5 (d, $J$ = 8.2 Hz), 116.4 (d, $J$ = 23.2 Hz).

**2-(4-Chlorophenoxy)benzoic acid, 1c, Scheme 2.** The same general procedure was followed by using 2-iodobenzoic acid (1.55 g, 6.2 mmol, 1.0 equiv.) and 4-chlorophenol (1.60 g, 12.4 mmol, 2.0 equiv.). Column chromatography ($SiO_2$, eluting with 7 : 3 hexane–ethyl acetate) afforded the desired product as a white solid, (1.3 g, 84%), mp 115–117 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 7.85 (dd, $J$ = 7.5 Hz, 1.5 Hz, 1H), 7.60 (td, $J$ = 8.1 Hz, 1.8 Hz, 1H), 7.36–7.41 (m, 2H), 7.31 (td, $J$ = 8.1 Hz, 0.6 Hz, 1H), 7.08 (d, $J$ = 8.1 Hz, 1H), 6.87–6.92 (m, 2H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 166.4, 156.7, 154.3, 133.8, 131.6, 129.7, 126.5, 124.74, 124.67, 121.6, 119.0; IR (neat): $\nu_{max}$ 1690, 1484, 1313, 1244, 1091, 826 cm$^{-1}$; HRMS (ESI, $m/z$) calcd for $C_{13}H_9ClO_3Na$ $[M + Na]^+$: 271.0138; found: 271.0130.

**2-(4-Bromophenoxy)benzoic acid, 1d, Scheme 2.**[9] The same general procedure was followed by using 2-iodobenzoic acid (1.55 g, 6.2 mmol, 1.0 equiv.) and 4-bromophenol (1.2 g, 12.4 mmol, 2.0 equiv.). Column chromatography ($SiO_2$, eluting with 7 : 3 hexane–ethyl acetate) afforded the desired product as a white solid, (1.27 g, 70%), mp 118–120 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 12.94 (br s, 1H), 7.86 (d, $J$ = 6.9 Hz, 1H), 7.60 (t, $J$ = 7.5 Hz, 1H), 7.50 (d, $J$ = 8.7 Hz, 2H), 7.32 (t, $J$ = 7.5 Hz, 1H), 7.09 (d, $J$ = 8.1 Hz, 1H), 6.84 (d, $J$ = 9.0 Hz, 2H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 166.3, 157.2, 154.2, 133.8, 132.6, 131.6, 124.7, 121.7, 119.3, 114.2.

**2-(4-Methoxyphenoxy)benzoic acid, 1e, Scheme 2.**[9] The same general procedure was followed by using 2-iodobenzoic acid (1.55 g, 6.2 mmol, 1.0 equiv.) and 4-methoxyphenol (1.54 g, 12.4 mmol, 2.0 equiv.). Column chromatography ($SiO_2$, eluting with 6 : 4 hexane–ethyl acetate) afforded the desired product as a white solid, (1.29 g, 85%), mp 143–145 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 7.77 (dd, $J$ = 7.5 Hz, 1.5 Hz, 1H), 7.48 (td, $J$ = 8.4 Hz, 1.5 Hz, 1H), 7.17 (t, $J$ = 7.5 Hz, 1H), 6.89–6.95 (m, 4H), 6.84 (d, $J$ = 8.1 Hz, 1H), 3.72 (s, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 167.1, 156.4, 155.5, 150.3, 133.4, 131.3, 123.8, 123.1, 120.0, 119.2, 115.2, 55.6.

**2-(4-(Benzyloxy)phenoxy)benzoic acid, 1f, Scheme 2.** The same general procedure was followed by using 2-iodobenzoic acid (1.55 g, 6.2 mmol, 1.0 equiv.) and 4-(benzyloxy)phenol (2.48 g, 12.4 mmol, 2.0 equiv.). Column chromatography ($SiO_2$, eluting with 6 : 4 hexane–ethyl acetate) afforded the desired product as a white solid, (1.47 g, 74%), mp 153–155 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 12.85 (br s, 1H), 7.78 (dd, $J$ = 7.5 Hz, 1.2 Hz, 1H), 7.31–7.52 (m, 6H), 7.18 (t, $J$ = 7.5 Hz, 1H), 7.02 (d, $J$ = 9.0 Hz, 2H), 6.92 (d, $J$ = 9.0 Hz, 2H), 6.87 (d, $J$ = 8.4 Hz, 1H), 5.07 (s, 2H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 166.8, 156.3, 154.5, 150.4, 137.1, 133.3, 131.3, 128.5, 127.9, 127.8, 123.7, 123.0, 119.9, 119.2, 116.0, 69.7; IR (neat): $\nu_{max}$ 1684, 1503, 1311, 1216, 1019, 784 cm$^{-1}$; HRMS (ESI, $m/z$) calcd for $C_{20}H_{16}O_4Na$ $[M + Na]^+$: 343.0946; found: 343.0950.

**2-(*p*-Tolyloxy)benzoic acid, 1g, Scheme 2.**[9] The same general procedure was followed by using 2-iodobenzoic acid (1.55 g, 6.2 mmol, 1.0 equiv.) and *p*-cresol (1.34 g, 12.4 mmol, 2.0 equiv.). Column chromatography ($SiO_2$, eluting with 7 : 3 hexane–ethyl acetate) afforded the desired product as a white solid, (1.13 g, 80%), mp 122–124 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 7.80 (dd, $J$ = 7.8 Hz, 1.5 Hz, 1H), 7.52 (td, $J$ = 8.4 Hz, 1.5 Hz, 1H), 7.22 (td, $J$ = 7.5 Hz, 0.6 Hz, 1H), 7.16 (d, $J$ = 8.1 Hz, 2H), 6.93 (d, $J$ = 8.1 Hz, 1H), 6.82 (d, $J$ = 8.4 Hz, 2H), 2.27 (s, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 166.7, 155.5, 155.0, 133.4, 132.1, 131.3, 130.3, 124.2, 123.5, 120.3, 118.0, 20.3.

**4-Diphenyl-2-phenoxybenzoic acid, 1h, Scheme 2.** The same general procedure was followed by using 2-iodobenzoic acid (1.55 g, 6.2 mmol, 1.0 equiv.) and 4-phenylphenol (2.11 g, 12.4 mmol, 2.0 equiv.). Column chromatography ($SiO_2$, eluting with 7 : 3 hexane–ethyl acetate) afforded the desired product as a white solid, (1.48 g, 82%), mp 149–151 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 12.94 (br s, 1H), 7.86 (d, $J$ = 7.5 Hz, 1H), 7.58–7.65 (m, 5H), 7.44 (t, $J$ = 7.5 Hz, 2H), 7.28–7.35 (m, 2H), 7.10 (d, $J$ = 8.1 Hz, 1H), 6.97 (d, $J$ = 8.4 Hz, 2H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 167.0, 157.8, 155.1, 140.0, 135.2, 134.2, 132.0, 129.4, 128.6, 127.6, 126.9, 125.2, 124.8, 122.0, 118.0; IR (neat): $\nu_{max}$ 1689, 1482, 1312, 1220, 758 cm$^{-1}$; HRMS (ESI, $m/z$) calcd for $C_{19}H_{14}O_3Na$ $[M + Na]^+$: 313.0841; found: 313.0838.

**2-(Naphthalen-3-yloxy)benzoic acid, 1i, Scheme 2.**[9] The same general procedure was followed by using 2-iodobenzoic acid (1.55 g, 6.2 mmol, 1.0 equiv.) and naphthalen-2-ol (1.79 g, 12.4 mmol, 2.0 equiv.). Column chromatography ($SiO_2$, eluting with 7 : 3 hexane–ethyl acetate) afforded the desired product as a white solid, (1.31 g, 80%), mp 118–120 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 7.94 (d, $J$ = 9.0 Hz, 1H), 7.89 (d, $J$ = 7.5 Hz, 2H), 7.77 (d, $J$ = 7.8 Hz, 1H), 7.60 (t, $J$ = 8.1 Hz, 1H), 7.39–7.49 (m, 2H), 7.25–7.35 (m, 2H), 7.20 (s, 1H), 7.12 (d, $J$ = 8.4 Hz, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 166.6, 155.6, 154.8, 134.0, 133.8, 131.6, 130.0, 129.6, 127.7, 127.0, 126.7, 124.72, 124.67, 124.4, 121.5, 119.3, 112.1.

**2-(*o*-Tolyloxy)benzoic acid, 1k, Scheme 2.**[9] The same general procedure was followed by using 2-iodobenzoic acid (1.55 g, 6.2 mmol, 1.0 equiv.) and *o*-cresol (1.3 mL, 12.4 mmol, 2.0 equiv.). Column chromatography ($SiO_2$, eluting with 7 : 3 hexane–ethyl acetate) afforded the desired product as a white solid, (990 mg, 70%), mp 122–124 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 12.86 (br s, 1H), 7.81 (dd, $J$ = 7.8 Hz, 1.5 Hz, 1H), 7.50 (td, $J$ = 8.7 Hz, 1.8 Hz, 1H), 7.30 (d, $J$ = 7.2 Hz, 1H), 7.15–7.22 (m, 2H), 7.06 (t, $J$ = 7.5 Hz, 1H), 6.80 (d, $J$ = 8.1 Hz, 1H), 6.73 (d, $J$ = 7.8 Hz, 1H), 2.30 (s, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 167.1, 156.0, 155.0, 133.8, 131.8, 128.9, 127.7, 124.0, 123.8, 123.4, 119.2, 118.4, 16.2.

**2-(2-Methoxyphenoxy)benzoic acid, 1l, Scheme 2.** The same general procedure was followed by using 2-iodobenzoic acid (1.55 g, 6.2 mmol, 1.0 equiv.) and 2-methoxyphenol (1.54 g, 12.4 mmol, 2.0 equiv.). Column chromatography ($SiO_2$, eluting with 6 : 4 hexane–ethyl acetate) afforded the desired product as a white solid, (1.09 g, 72%), mp 114–116 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 12.82 (br s, 1H), 7.77 (d, $J$ = 7.5 Hz, 1H), 7.43 (t, $J$ = 7.2 Hz, 1H), 7.09–7.21 (m, 3H), 6.92–6.98 (m, 2H), 6.65 (d, $J$ = 8.4 Hz, 1H), 3.74 (s, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 166.8, 156.5, 151.0, 144.1, 133.2, 131.2, 125.3, 122.3, 122.2, 121.2, 120.8, 117.0, 113.5, 55.7; IR (neat): $\nu_{max}$ 1666, 1494, 1306, 1260, 749 cm$^{-1}$; HRMS (ESI, $m/z$) calcd for $C_{14}H_{12}O_4Na$ $[M + Na]^+$: 267.0633; found: 267.0628.

**2-(3-Chlorophenoxy)benzoic acid, 1m, Scheme 2.** The same general procedure was followed by using 2-iodobenzoic acid (1.55 g, 6.2 mmol, 1.0 equiv.) and 3-chlorophenol (1.33 mL, 12.4 mmol, 2.0 equiv.). Column chromatography ($SiO_2$, eluting with 7 : 3 hexane–ethyl acetate) afforded the desired product as a white solid, (1.09 g, 71%), mp 98–100 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 12.97 (br s, 1H), 7.88 (d, $J$ = 7.8 Hz, 1H), 7.63 (t, $J$ = 7.5 Hz, 1H), 7.32–7.39 (m, 2H), 7.14 (d, $J$ = 7.8 Hz, 2H), 6.92 (s, 1H), 6.83 (dd, $J$ = 8.4 Hz, 2.1 Hz, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 166.2, 158.9, 153.8, 133.9, 133.8, 131.6, 131.2, 125.0, 124.9, 122.5, 122.1, 117.0, 115.7; IR (neat): $\nu_{max}$ 1693, 1593, 1468, 1417, 1239, 913, 763 cm$^{-1}$; HRMS (ESI, $m/z$) calcd for $C_{13}H_9ClO_3Na$ $[M + Na]^+$: 271.0138; found: 271.0134.

**2-(3-Methoxyphenoxy)benzoic acid, 1n, Scheme 2.**[24] The same general procedure was followed by using 2-iodobenzoic acid (1.55 g, 6.2 mmol, 1.0 equiv.) and 3-methoxyphenol (1.54 g, 12.4 mmol, 2.0 equiv.). Column chromatography ($SiO_2$, eluting with 6 : 4 hexane–ethyl acetate) afforded the desired product as a white solid, (1.14 g, 75%), mp 118–120 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 7.82 (d, $J$ = 7.5 Hz, 1H), 7.57 (t, $J$ = 7.2 Hz, 1H), 7.21–7.30 (m, 2H), 7.03 (d, $J$ = 8.1 Hz, 1H), 6.67 (dd, $J$ = 8.1 Hz, 1.2 Hz, 1H), 6.49 (s, 1H), 6.42 (d, $J$ = 8.1 Hz, 1H), 3.72 (s, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 166.6, 160.7, 158.7, 154.7, 133.4, 131.4, 130.4, 124.6, 124.1, 121.2, 109.6, 108.5, 103.9, 55.3.

**4-Chloro-2-phenoxybenzoic acid, 1r, Scheme 2.** The same general procedure was followed by using 2,4-dichlorobenzoic acid (1.18 g, 6.2 mmol, 1.0 equiv.) and phenol (1.2 g, 12.4 mmol, 2.0 equiv.). Column chromatography ($SiO_2$, eluting with 7 : 3 hexane–ethyl acetate) afforded the desired product as a white solid, (462 mg, 30%), mp 155–157 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 7.86 (d, $J$ = 8.1 Hz, 1H), 7.32–7.42 (m, 3H), 7.15 (t, $J$ = 7.2 Hz, 1H), 6.99 (t, $J$ = 7.8 Hz, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 157.0, 156.7, 156.6, 137.8, 133.8, 130.5, 124.4, 124.1, 120.7, 118.6, 100.0; IR (neat): $\nu_{max}$ 1675, 1591, 1482, 1308, 1229, 919 cm$^{-1}$; HRMS (ESI, $m/z$) calcd for $C_{13}H_9ClO_3Na$ $[M + Na]^+$: 271.0138; found: 271.0125.

**5-Nitro-2-phenoxybenzoic acid, 1t, Scheme 2.** The same general procedure was followed by using 2-bromo-5-nitrobenzoic acid (1.52 g, 6.2 mmol, 1.0 equiv.) and phenol (1.2 g, 12.4 mmol, 2.0 equiv.). Column chromatography ($SiO_2$, eluting with 6 : 4 hexane–ethyl acetate) afforded the desired product as a white solid, (804 mg, 50%), mp 160–162 °C. $^1$H NMR (600 MHz, DMSO-$d_6$): $\delta$ 8.58 (d, $J$ = 3.0 Hz, 1H), 8.33 (dd, $J$ = 9.0 Hz, 3.0 Hz, 1H), 7.48 (t, $J$ = 7.8 Hz, 2H), 7.27 (t, $J$ = 7.8 Hz, 1H), 7.14 (t, $J$ = 7.8 Hz, 2H), 7.00 (d, $J$ = 9.0 Hz, 1H); $^{13}$C NMR (150 MHz, DMSO-$d_6$): $\delta$ 165.3, 161.5, 155.3, 142.3, 130.9, 129.0, 127.4, 125.6, 123.8, 120.3, 119.2; IR (neat): $\nu_{max}$ 1691, 1614, 1479, 1348, 1257, 745 cm$^{-1}$; HRMS (ESI, $m/z$) calcd for $C_{13}H_9NO_5Na$ $[M + Na]^+$: 282.0378; found: 282.0401.

**2-(4-Chlorophenoxy)-5-nitrobenzoic acid, 1u, Scheme 2.** The same general procedure was followed by using 2-bromo-5-nitrobenzoic acid (1.52 g, 6.2 mmol, 1.0 equiv.) and 4-chlorophenol (1.60 g, 12.4 mmol, 2.0 equiv.). Column chromatography ($SiO_2$, eluting with 6 : 4 hexane–ethyl acetate) afforded the desired product as a white solid, (838 mg, 46%), mp 159–161 °C. $^1$H NMR (600 MHz, DMSO-$d_6$): $\delta$ 8.60 (d, $J$ = 2.4 Hz, 1H), 8.35 (dd, $J$ = 9.0 Hz, 3.0 Hz, 1H), 7.50–7.53 (m, 2H), 7.15–7.18 (m, 2H), 7.11 (d, $J$ = 9.0 Hz, 1H); $^{13}$C NMR (150 MHz, DMSO-$d_6$): $\delta$ 165.1, 160.9, 154.5, 142.7, 130.7, 129.3, 129.1, 127.5, 124.1, 121.8, 120.1; IR (neat): $\nu_{max}$ 1707, 1478, 1345, 845 cm$^{-1}$; HRMS (EI, $m/z$) calcd for $C_{13}H_8ClNO_5Na$ $[M]^+$: 315.9989; found: 315.9986.

**5-Methoxy-2-phenoxybenzoic acid, 1v, Scheme 2.** The same general procedure was followed by using 2-bromo-5-methoxybenzoic acid (1.43 g, 6.2 mmol, 1.0 equiv.) and Phenol (1.2 g, 12.4 mmol, 2.0 equiv.). Column chromatography ($SiO_2$, eluting with 6 : 4 hexane–ethyl acetate) afforded the desired product as a white solid, (760 mg, 50%), mp 142–144 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 7.26–7.31 (m, 3H), 7.15 (dd, $J$ = 8.7 Hz, 2.4 Hz, 1H), 6.97–7.04 (m, 2H), 6.80 (d, $J$ = 7.8 Hz, 2H), 3.78 (s, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 166.3, 158.8, 155.6, 147.6, 129.8, 126.0, 123.8, 122.1, 119.5, 116.5, 115.3, 55.7; IR (neat): $\nu_{max}$ 1692, 1598, 1482, 1275, 1218, 746 cm$^{-1}$; HRMS (ESI, $m/z$) calcd for $C_{14}H_{12}O_4Na$ $[M + Na]^+$: 267.0633; found: 267.0635.

For the experimental procedure for the preparation of compounds **1o**, **1p**, **1q**, **1j**, **1s**, **1w**, **3a**, **3b**, **3c**, **3d**, **3e** and **3f** see the ESI.†

### General experimental procedure for the carboxyl radical-assisted 1,5-aryl migration through Smiles rearrangement using 2-phenoxybenzoic acids, Scheme 2

To an oven-dried 15 mL sealed tube, a mixture of 2-phenoxybenzoic acids (0.1 mmol, 1.0 equiv.), silver nitrate (0.9 mg, 0.005 mmol), potassium persulfate (40.5 mg, 0.15 mmol, 1.5 equiv.) and potassium trifluoroacetate (30.5 mg, 0.2 mmol, 2.0 equiv.) was taken and dry MeCN (2.0 mL) was added to it. After

flushing with nitrogen, the vessel was sealed with a screw cap. The reaction mixture was allowed to stir for 36 h at 130 °C. After completion (as indicated by TLC), the reaction mixture was cooled to room temperature. Then the reaction mixture was poured into water (20 mL) and extracted with ethyl acetate (20 mL). The organic layer was washed with water (10 mL) and brine (10 mL), dried over anhydrous $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography using ethyl acetate–hexane as eluent to afford the desired product.

**Phenyl 2-hydroxybenzoate, 2a, Scheme 2.**[25] The same general procedure was followed by using 2-phenoxybenzoic acid (21.5 mg, 0.1 mmol, 1.0 equiv.), silver nitrate (0.9 mg, 0.005 mmol), potassium persulfate (40.5 mg, 0.15 mmol, 1.5 equiv.) and potassium trifluoroacetate (30.5 mg, 0.2 mmol, 2.0 equiv.). Column chromatography ($SiO_2$, eluting with 96 : 4 hexane–ethyl acetate) afforded the desired product as a colourless oil, (14 mg, 64%). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 10.53 (s, 1H), 8.10 (d, $J$ = 7.8 Hz, 1H), 7.56 (t, $J$ = 8.4 Hz, 1H), 7.48 (t, $J$ = 8.4 Hz, 2H), 7.34 (t, $J$ = 7.2 Hz, 1H),7.24 (d, $J$ = 8.4 Hz, 2H), 7.07 (d, $J$ = 8.4 Hz, 1H), 7.00 (t, $J$ = 7.2 Hz, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 168.9, 162.2, 150.1, 136.5, 130.3, 129.6, 126.4, 121.6, 119.4, 117.8, 111.8.

**4-Fluorophenyl 2-hydroxybenzoate, 2b, Scheme 2.** The same general procedure was followed by using 2-(4-fluorophenoxy) benzoic acid (23.5 mg, 0.1 mmol, 1.0 equiv.), silver nitrate (0.9 mg, 0.005 mmol), potassium persulfate (40.5 mg, 0.15 mmol, 1.5 equiv.) and potassium trifluoroacetate (30.5 mg, 0.2 mmol, 2.0 equiv.). Column chromatography ($SiO_2$, eluting with 96 : 4 hexane–ethyl acetate) afforded the desired product as a colourless oil, (12.5 mg, 54%). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 10.45 (s, 1H), 8.08 (dd, $J$ = 7.8 Hz, 1.2 Hz, 1H), 7.55–7.58 (m, 1H), 7.19–7.21 (m, 2H), 7.14–7.17 (m, 2H), 7.06 (d, $J$ = 8.4 Hz, 1H), 7.00 (t, $J$ = 7.8 Hz, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 168.9, 162.2, 160.5 (d, $J$ = 244.5 Hz), 145.8 (d, $J$ = 3.0 Hz), 136.6, 130.3, 123.1 (d, $J$ = 7.5 Hz), 119.5, 117.9, 116.3 (d, $J$ = 24.0 Hz), 111.6; IR (neat): $\nu_{max}$ 3230, 1692, 1504, 1300, 1182, 1064, 757 cm$^{-1}$; HRMS (ESI, $m/z$) calcd for $C_{13}H_9FO_3Na$ $[M + Na]^+$: 255.0433; found: 255.0451.

**4-Chlorophenyl 2-hydroxybenzoate, 2c, Scheme 2.**[26] The same general procedure was followed by using 2-(4-chlorophenoxy)benzoic acid (25.0 mg, 0.1 mmol, 1.0 equiv.), silver nitrate (0.9 mg, 0.005 mmol), potassium persulfate (40.5 mg, 0.15 mmol, 1.5 equiv.) and potassium trifluoroacetate (30.5 mg, 0.2 mmol, 2.0 equiv.). Column chromatography ($SiO_2$, eluting with 96 : 4 hexane–ethyl acetate) afforded the desired product as a white solid, (15 mg, 60%), mp 98–100 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 10.39 (s, 1H), 8.05 (dd, $J$ = 8.1 Hz, 1.5 Hz, 1H), 7.52–7.58 (m, 1H), 7.42 (d, $J$ = 8.7 Hz, 2H), 7.16 (d, $J$ = 9.0 Hz, 2H), 7.04 (d, $J$ = 8.4 Hz, 1H), 6.97 (t, $J$ = 7.8 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 168.6, 162.2, 148.5, 136.7, 131.8, 130.3, 129.7, 123.0, 119.6, 117.9, 111.5; IR (neat): $\nu_{max}$ 3256, 1686, 1486, 1304, 1195, 755 cm$^{-1}$; HRMS (ESI, $m/z$) calcd for $C_{13}H_9ClO_3Na$ $[M + Na]^+$: 271.0138; found: 271.0145.

**4-Bromophenyl 2-hydroxybenzoate, 2d, Scheme 2.** The same general procedure was followed by using 2-(4-bromophenoxy) benzoic acid (29.5 mg, 0.1 mmol, 1.0 equiv.), silver nitrate (0.9 mg, 0.005 mmol), potassium persulfate (40.5 mg, 0.15 mmol, 1.5 equiv.) and potassium trifluoroacetate (30.5 mg, 0.2 mmol, 2.0 equiv.). Column chromatography ($SiO_2$, eluting with 96 : 4 hexane–ethyl acetate) afforded the desired product as a white solid, (13.5 mg, 46%), mp 67–69 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 10.40 (s, 1H), 8.07 (dd, $J$ = 8.4 Hz, 1.2 Hz, 1H), 7.55–7.60 (m, 3H), 7.13 (d, $J$ = 9.0 Hz, 2H), 7.06 (d, $J$ = 8.4 Hz, 1H), 6.99 (t, $J$ = 7.2 Hz, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 168.5, 162.2, 149.1, 136.7, 132.7, 130.3, 123.4, 119.5, 117.9, 111.5; IR (neat): $\nu_{max}$ 3221, 1689, 1506, 1299, 1188, 1067, 755 cm$^{-1}$; HRMS (EI, $m/z$) calcd for $C_{13}H_9BrO_4$ $[M]^+$: 291.9735, 293.9715; found: 291.9738, 293.9727.

**4-Methoxyphenyl 2-hydroxybenzoate, 2e, Scheme 2.**[26] The same general procedure was followed by using 2-(4-methoxyphenoxy)benzoic acid (24.5 mg, 0.1 mmol, 1.0 equiv.), silver nitrate (0.9 mg, 0.005 mmol), potassium persulfate (40.5 mg, 0.15 mmol, 1.5 equiv.) and potassium trifluoroacetate (30.5 mg, 0.2 mmol, 2.0 equiv.). Column chromatography ($SiO_2$, eluting with 95 : 5 hexane–ethyl acetate) afforded the desired product as a colourless oil, (14.5 mg, 60%). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 10.56 (s, 1H), 8.09 (dd, $J$ = 7.8 Hz, 1.8 Hz, 1H), 7.54–7.57 (m, 1H), 7.13–7.16 (m, 2H), 7.06 (dd, $J$ = 8.4 Hz, 0.6 Hz, 1H), 6.96–7.00 (m, 3H), 3.85 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 169.3, 162.1, 157.6, 143.4, 136.4, 130.3, 122.4, 119.4, 117.8, 114.6, 111.9, 55.6; IR (neat): $\nu_{max}$ 3221, 1689, 1506, 1299, 1188, 1067, 755 cm$^{-1}$; HRMS (EI, $m/z$) calcd for $C_{14}H_{12}O_4$ $[M]^+$: 244.0736; found: 244.0738.

**4-(Benzyloxy)phenyl 2-hydroxybenzoate, 2f, Scheme 2.** The same general procedure was followed by using 2-(4-(benzyloxy) phenoxy)benzoic acid (32.0 mg, 0.1 mmol, 1.0 equiv.), silver nitrate (0.9 mg, 0.005 mmol), potassium persulfate (40.5 mg, 0.15 mmol, 1.5 equiv.) and potassium trifluoroacetate (30.5 mg, 0.2 mmol, 2.0 equiv.). Column chromatography ($SiO_2$, eluting with 95 : 5 hexane–ethyl acetate) afforded the desired product as a white solid, (19.5 mg, 61%), mp 98–100 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 10.56 (s, 1H), 8.09 (dd, $J$ = 7.8 Hz, 1.8 Hz, 1H), 7.56 (td, $J$ = 8.4 Hz, 1.2 Hz, 1H), 7.47 (d, $J$ = 7.2 Hz, 2H), 7.43 (t, $J$ = 7.2 Hz, 2H), 7.37 (t, $J$ = 7.2 Hz, 1H), 7.14–7.16 (m, 2H), 7.05–7.07 (m, 3H), 6.99 (t, $J$ = 7.8 Hz, 1H), 5.11 (s, 2H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 169.2, 162.1, 156.9, 143.6, 136.7, 136.4, 130.3, 128.6, 128.1, 127.5, 122.4, 119.4, 117.8, 115.6, 111.9, 70.4; IR (neat): $\nu_{max}$ 3264, 1693, 1505, 1299, 1196, 749 cm$^{-1}$; HRMS (ESI, $m/z$) calcd for $C_{20}H_{16}O_4Na$ $[M + Na]^+$: 343.0946; found: 343.0938.

***p*-Tolyl 2-hydroxybenzoate, 2g, Scheme 2.**[26] The same general procedure was followed by using 2-(*p*-tolyloxy)benzoic acid (23.0 mg, 0.1 mmol, 1.0 equiv.), silver nitrate (0.9 mg, 0.005 mmol), potassium persulfate (40.5 mg, 0.15 mmol, 1.5 equiv.) and potassium trifluoroacetate (30.5 mg, 0.2 mmol, 2.0 equiv.). Column chromatography ($SiO_2$, eluting with 96 : 4 hexane–ethyl acetate) afforded the desired product as a colourless oil, (12.5 mg, 54%). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 10.56 (s, 1H), 8.09 (d, $J$ = 7.8 Hz, 1H), 7.55 (t, $J$ = 8.4 Hz, 1H), 7.26–7.28 (m, 2H), 7.11 (d, $J$ = 8.4 Hz, 2H), 7.06 (d, $J$ = 8.4 Hz,

1H), 6.99 (t, $J$ = 7.8 Hz, 1H), 2.40 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 169.1, 162.1, 147.8, 136.4, 136.1, 130.3, 130.1, 121.3, 119.4, 117.8, 111.9, 20.9; IR (neat): $\nu_{max}$ 3216, 1690, 1482, 1300, 1193, 757 cm$^{-1}$; HRMS (EI, $m/z$) calcd for $C_{14}H_{12}O_3$ $[M]^+$: 228.0786; found: 228.0778.

**4-Diphenyl 2-hydroxybenzoate, 2h, Scheme 2.** The same general procedure was followed by using 2-(4-phenylphenoxy) benzoic acid (29.0 mg, 0.1 mmol, 1.0 equiv.), silver nitrate (0.9 mg, 0.005 mmol), potassium persulfate (40.5 mg, 0.15 mmol, 1.5 equiv.) and potassium trifluoroacetate (30.5 mg, 0.2 mmol, 2.0 equiv.). Column chromatography ($SiO_2$, eluting with 96 : 4 hexane–ethyl acetate) afforded the desired product as a white solid, (15 mg, 52%), mp 100–102 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 10.53 (s, 1H), 8.12 (d, $J$ = 7.8 Hz, 1H), 7.68 (d, $J$ = 7.8 Hz, 2H), 7.62 (d, $J$ = 7.8 Hz, 2H), 7.58 (t, $J$ = 7.8 Hz, 1H), 7.48 (t, $J$ = 7.2 Hz, 2H), 7.39 (t, $J$ = 7.2 Hz, 1H), 7.31 (d, $J$ = 8.4 Hz, 2H), 7.08 (d, $J$ = 8.4 Hz, 1H), 7.01 (t, $J$ = 7.2 Hz, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 169.0, 162.2, 149.4, 140.2, 139.6, 136.5, 130.4, 128.8, 128.3, 127.5, 127.1, 121.9, 119.5, 117.8, 111.8; IR (neat): $\nu_{max}$ 3208, 1688, 1483, 1301, 1178, 757, 691 cm$^{-1}$; HRMS (ESI, $m/z$) calcd for $C_{19}H_{14}O_3Na$ $[M + Na]^+$: 313.0841; found: 313.0856.

**Naphthalen-2-yl 2-hydroxybenzoate, 2i, Scheme 2.** The same general procedure was followed by using 2-(naphthalen-3-yloxy)benzoic acid (26.5 mg, 0.1 mmol, 1.0 equiv.), silver nitrate (0.9 mg, 0.005 mmol), potassium persulfate (40.5 mg, 0.15 mmol, 1.5 equiv.) and potassium trifluoroacetate (30.5 mg, 0.2 mmol, 2.0 equiv.). Column chromatography ($SiO_2$, eluting with 96 : 4 hexane–ethyl acetate) afforded the desired product as a white solid, (16.5 mg, 63%), mp 86–88 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 10.55 (s, 1H), 8.17 (dd, $J$ = 7.8 Hz, 1.2 Hz, 1H), 7.95 (d, $J$ = 9.0 Hz, 1H), 7.91 (d, $J$ = 7.8 Hz, 1H), 7.87 (d, $J$ = 7.8 Hz, 1H), 7.71 (d, $J$ = 2.4 Hz, 1H), 7.52–7.60 (m, 3H), 7.37 (dd, $J$ = 9.0 Hz, 2.4 Hz, 1H), 7.09 (d, $J$ = 8.4 Hz, 1H), 7.02 (t, $J$ = 7.8 Hz, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 169.1, 162.2, 147.7, 136.5, 133.7, 131.7, 130.4, 129.6, 127.8, 127.7, 126.8, 126.0, 120.9, 119.5, 118.8, 117.9, 111.8; IR (neat): $\nu_{max}$ 3252, 1688, 1479, 1297, 1156, 756 cm$^{-1}$; HRMS (ESI, $m/z$) calcd for $C_{17}H_{12}O_3Na$ $[M + Na]^+$: 287.0684; found: 287.0675.

**Naphthalen-1-yl 2-hydroxybenzoate, 2j, Scheme 2.** The same general procedure was followed by using 2-(naphthalen-1-yloxy)benzoic acid (26.5 mg, 0.1 mmol, 1.0 equiv.), silver nitrate (0.9 mg, 0.005 mmol), potassium persulfate (40.5 mg, 0.15 mmol, 1.5 equiv.) and potassium trifluoroacetate (30.5 mg, 0.2 mmol, 2.0 equiv.). Column chromatography ($SiO_2$, eluting with 96 : 4 hexane–ethyl acetate) afforded the desired product as a colourless oil, (16.4 mg, 62%). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 10.52 (s, 1H), 8.32 (dd, $J$ = 7.8 Hz, 1.8 Hz, 1H), 7.93–7.96 (m, 2H), 7.86 (d, $J$ = 8.4 Hz, 1H), 7.62–7.64 (m, 1H), 7.54–7.59 (m, 3H), 7.40 (dd, $J$ = 7.8 Hz, 1.2 Hz, 1H), 7.12 (dd, $J$ = 8.4 Hz, 0.6 Hz, 1H), 7.08 (td, $J$ = 7.8 Hz, 1.2 Hz, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 169.0, 162.3, 146.0, 136.7, 134.7, 130.4, 128.1, 126.8, 126.72, 126.67, 126.6, 125.4, 121.0, 119.6, 118.2, 118.0, 111.7; IR (neat): $\nu_{max}$ 3231, 2927, 1693, 1481, 1296, 1205, 761 cm$^{-1}$; HRMS (ESI, $m/z$) calcd for $C_{17}H_{12}O_3Na$ $[M + Na]^+$: 287.0684; found: 287.0669.

***o*-Tolyl 2-hydroxybenzoate, 2k, Scheme 2.**[26] The same general procedure was followed by using 2-(*o*-tolyloxy)benzoic acid (23.0 mg, 0.1 mmol, 1.0 equiv.), silver nitrate (0.9 mg, 0.005 mmol), potassium persulfate (40.5 mg, 0.15 mmol, 1.5 equiv.) and potassium trifluoroacetate (30.5 mg, 0.2 mmol, 2.0 equiv.). Column chromatography ($SiO_2$, eluting with 96 : 4 hexane–ethyl acetate) afforded the desired product as a colourless oil, (12 mg, 52%). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 10.56 (s, 1H), 8.13 (dd, $J$ = 7.8 Hz, 1.8 Hz, 1H), 7.57 (td, $J$ = 9.0 Hz, 1.8 Hz, 1H), 7.31–7.33 (m, 1H), 7.29 (d, $J$ = 7.8 Hz, 1H), 7.24 (td, $J$ = 7.8 Hz, 1.2 Hz, 1H), 7.15 (d, $J$ = 7.8 Hz, 1H), 7.07 (dd, $J$ = 8.4 Hz, 0.6 Hz, 1H), 7.01 (td, $J$ = 7.8 Hz, 0.6 Hz, 1H), 2.26 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 168.7, 162.2, 148.7, 136.4, 131.3, 130.29, 130.26, 127.1, 126.5, 121.8, 119.5, 117.8, 111.7, 16.2; IR (neat): $\nu_{max}$ 3214, 2926, 1689, 1584, 1486, 1299, 1165, 753 cm$^{-1}$; HRMS (ESI, $m/z$) calcd for $C_{14}H_{12}O_3Na$ $[M + Na]^+$: 251.0684; found: 251.0672.

**2-Methoxyphenyl 2-hydroxybenzoate, 2l, Scheme 2.**[26] The same general procedure was followed by using 2-(2-methoxyphenoxy)benzoic acid (24.5 mg, 0.1 mmol, 1.0 equiv.), silver nitrate (0.9 mg, 0.005 mmol), potassium persulfate (40.5 mg, 0.15 mmol, 1.5 equiv.) and potassium trifluoroacetate (30.5 mg, 0.2 mmol, 2.0 equiv.). Column chromatography ($SiO_2$, eluting with 95 : 5 hexane–ethyl acetate) afforded the desired product as a white solid, (14 mg, 57%), mp 64–66 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 10.51 (s, 1H), 8.13 (dd, $J$ = 7.8 Hz, 1.2 Hz, 1H), 7.54–7.57 (m, 1H), 7.30 (td, $J$ = 8.4 Hz, 1.8 Hz, 1H), 7.18 (dd, $J$ = 7.8 Hz, 1.2 Hz, 1H), 7.02–7.06 (m, 3H), 6.99 (t, $J$ = 7.8 Hz, 1H), 3.85 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 168.4, 162.0, 151.1, 139.0, 136.3, 130.6, 127.4, 122.8, 120.8, 119.4, 117.7, 112.5, 111.8, 55.9; IR (neat): $\nu_{max}$ 3212, 1692, 1499, 1296, 754 cm$^{-1}$; HRMS (ESI, $m/z$) calcd for $C_{14}H_{12}O_4Na$ $[M + Na]^+$: 267.0633; found: 267.0625.

**3-Chlorophenyl 2-hydroxybenzoate, 2m, Scheme 2.** The same general procedure was followed by using 2-(3-chlorophenoxy)benzoic acid (25.0 mg, 0.1 mmol, 1.0 equiv.), silver nitrate (0.9 mg, 0.005 mmol), potassium persulfate (40.5 mg, 0.15 mmol, 1.5 equiv.) and potassium trifluoroacetate (30.5 mg, 0.2 mmol, 2.0 equiv.). Column chromatography ($SiO_2$, eluting with 96 : 4 hexane–ethyl acetate) afforded the desired product as a colourless oil, (9.0 mg, 36%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 10.38 (s, 1H), 8.05 (d, $J$ = 8.1 Hz, 1.8 Hz, 1H), 7.56 (td, $J$ = 8.7 Hz, 1.8 Hz, 1H), 7.39 (t, $J$ = 7.8 Hz, 1H), 7.27–7.32 (m, 2H), 7.12–7.15 (m, 1H), 7.05 (d, $J$ = 8.4 Hz, 1H), 6.98 (td, $J$ = 8.4 Hz, 1.2 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 148.5, 162.2, 150.5, 136.7, 134.9, 130.32, 130.27, 126.7, 122.4, 120.1, 119.6, 117.9, 111.4; IR (neat): $\nu_{max}$ 3216, 1675, 1587, 1479, 1304, 753 cm$^{-1}$; HRMS (ESI, $m/z$) calcd for $C_{13}H_9ClO_3Na$ $[M + Na]^+$: 271.0138; found: 271.0153.

**3-Methoxyphenyl 2-hydroxybenzoate, 2n, Scheme 2.** The same general procedure was followed by using 2-(3-methoxyphenoxy)benzoic acid (24.5 mg, 0.1 mmol, 1.0 equiv.), silver nitrate (0.9 mg, 0.005 mmol), potassium persulfate (40.5 mg, 0.15 mmol, 1.5 equiv.) and potassium trifluoroacetate (30.5 mg, 0.2 mmol, 2.0 equiv.). Column chromatography ($SiO_2$, eluting with 95 : 5 hexane–ethyl acetate) afforded the

desired product as a colourless oil, (8.5 mg, 34%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 10.53 (s, 1H), 8.09 (dd, $J$ = 8.1 Hz, 1.5 Hz, 1H), 7.56 (td, $J$ = 8.7 Hz, 1.8 Hz, 1H), 7.37 (t, $J$ = 8.1 Hz, 1H), 7.07 (dd, $J$ = 7.8 Hz, 0.6 Hz, 1H), 7.00 (td, $J$ = 8.1 Hz, 0.9 Hz, 1H), 6.87–6.90 (m, 1H), 6.83 (dd, $J$ = 8.1 Hz, 1.2 Hz, 1H), 6.79 (t, $J$ = 2.1 Hz, 1H), 3.85 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 168.8, 162.2, 160.6, 151.0, 136.5, 130.3, 130.0, 119.5, 117.8, 113.8, 112.2, 111.8, 107.7, 55.5; IR (neat): $\nu_{max}$ 3224, 2927, 1691, 1610, 1486, 1143, 760 cm$^{-1}$; HRMS (ESI, $m/z$) calcd for $C_{14}H_{12}O_4Na$ $[M + Na]^+$: 267.0633; found: 267.0635.

**Phenyl 4-fluoro-2-hydroxybenzoate, 2o, Scheme 2.** The same general procedure was followed by using 4-fluoro-2-phenoxybenzoic acid (23.5 mg, 0.1 mmol, 1.0 equiv.), silver nitrate (0.9 mg, 0.005 mmol), potassium persulfate (40.5 mg, 0.15 mmol, 1.5 equiv.) and potassium trifluoroacetate (30.5 mg, 0.2 mmol, 2.0 equiv.). Column chromatography ($SiO_2$, eluting with 96 : 4 hexane–ethyl acetate) afforded the desired product as a colourless oil, (13.5 mg, 58%). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 10.76 (d, $J$ = 1.2 Hz, 1H), 8.11 (dd, $J$ = 9.0 Hz, 6.6 Hz, 1H), 7.48 (t, $J$ = 8.4 Hz, 2H), 7.34 (t, $J$ = 7.8 Hz, 1H), 7.22 (d, $J$ = 7.8 Hz, 2H), 6.75 (dd, $J$ = 10.2 Hz, $J$ = 2.4 Hz, 1H), 6.72 (td, $J$ = 8.4 Hz, 2.4 Hz, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 168.3, 167.7 (d, $J$ = 255.0 Hz), 164.3 (d, $J$ = 13.5 Hz), 149.9, 132.6 (d, $J$ = 12.0 Hz), 129.6, 126.5, 121.6, 108.6 (d, $J$ = 3.0 Hz), 107.8 (d, $J$ = 22.5 Hz), 104.6 (d, $J$ = 24.0 Hz); IR (neat): $\nu_{max}$ 3180, 1691, 1596, 1500, 1259, 1192, 771 cm$^{-1}$; HRMS (ESI, $m/z$) calcd for $C_{13}H_9FO_3Na$ $[M + Na]^+$: 255.0433; found: 255.0455.

***p*-Tolyl 4-fluoro-2-hydroxybenzoate, 2p, Scheme 2.** The same general procedure was followed by using 2-(*p*-tolyloxy)-4-fluorobenzoic acid (25.0 mg, 0.1 mmol, 1.0 equiv.), silver nitrate (0.9 mg, 0.005 mmol), potassium persulfate (40.5 mg, 0.15 mmol, 1.5 equiv.) and potassium trifluoroacetate (30.5 mg, 0.2 mmol, 2.0 equiv.). Column chromatography ($SiO_2$, eluting with 96 : 4 hexane–ethyl acetate) afforded the desired product as a white solid, (14.5 mg, 59%), mp 68–70 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 10.79 (d, $J$ = 1.8 Hz, 1H), 8.10 (dd, $J$ = 9.0 Hz, 6.6 Hz, 1H), 7.26 (d, $J$ = 8.4 Hz, 2H), 7.10 (d, $J$ = 8.4 Hz, 2H), 6.74 (dd, $J$ = 10.2 Hz, 2.4 Hz, 1H), 6.71 (td, $J$ = 8.4 Hz, 2.4 Hz, 1H), 2.40 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 168.5, 167.6 (d, $J$ = 253.5 Hz), 164.3 (d, $J$ = 15.0 Hz), 147.6, 136.2, 132.6 (d, $J$ = 12.0 Hz), 130.1, 121.2, 108.6 (d, $J$ = 3.0 Hz), 107.7 (d, $J$ = 24.0 Hz), 104.6 (d, $J$ = 24.0 Hz), 20.9; IR (neat): $\nu_{max}$ 3082, 1685, 1600, 1509, 1265, 1188, 767 cm$^{-1}$; HRMS (ESI, $m/z$) calcd for $C_{14}H_{11}FO_3Na$ $[M + Na]^+$: 269.0590; found: 269.0556.

**Naphthalen-2-yl 4-fluoro-2-hydroxybenzoate, 2q, Scheme 2.** The same general procedure was followed by using 4-fluoro-2-(naphthalen-3-yloxy)benzoic acid (28.5 mg, 0.1 mmol, 1.0 equiv.), silver nitrate (0.9 mg, 0.005 mmol), potassium persulfate (40.5 mg, 0.15 mmol, 1.5 equiv.) and potassium trifluoroacetate (30.5 mg, 0.2 mmol, 2.0 equiv.). Column chromatography ($SiO_2$, eluting with 96 : 4 hexane–ethyl acetate) afforded the desired product as a white solid, (17 mg, 60%), mp 78–80 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 10.77 (s, 1H), 8.17 (dd, $J$ = 9.0 Hz, 6.6 Hz, 1H), 7.95 (d, $J$ = 9.0 Hz, 1H), 7.91 (d, $J$ = 7.2 Hz, 1H), 7.86 (d, $J$ = 7.8 Hz, 1H), 7.70 (d, $J$ = 2.4 Hz, 1H), 7.52–7.57 (m, 2H), 7.36 (dd, $J$ = 9.0 Hz, 2.4 Hz, 1H), 6.77 (dd, $J$ = 10.2 Hz, 2.4 Hz, 1H), 6.74 (td, $J$ = 8.4 Hz, 2.4 Hz, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 168.5, 167.8 (d, $J$ = 255.0 Hz), 164.4 (d, $J$ = 13.5 Hz), 147.5, 133.7, 132.6 (d, $J$ = 10.5 Hz), 131.7, 129.7, 127.8, 127.7, 126.8, 126.1, 120.8, 118.8, 108.6 (d, $J$ = 1.5 Hz), 107.8 (d, $J$ = 22.5 Hz), 104.7 (d, $J$ = 2.4 Hz); IR (neat): $\nu_{max}$ 1677, 1506, 1262, 1205, 1152, 808 cm$^{-1}$; HRMS (ESI, $m/z$) calcd for $C_{17}H_{11}FO_3Na$ $[M + Na]^+$: 305.0590; found: 305.0598.

**Phenyl 4-chloro-2-hydroxybenzoate, 2r, Scheme 2.** The same general procedure was followed by using 4-chloro-2-phenoxybenzoic acid (25.0 mg, 0.1 mmol, 1.0 equiv.), silver nitrate (0.9 mg, 0.005 mmol), potassium persulfate (40.5 mg, 0.15 mmol, 1.5 equiv.) and potassium trifluoroacetate (30.5 mg, 0.2 mmol, 2.0 equiv.). Column chromatography ($SiO_2$, eluting with 96 : 4 hexane–ethyl acetate) afforded the desired product as a colourless oil, (14 mg, 57%). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 10.62 (s, 1H), 8.02 (d, J = 9.0 Hz, 1H), 7.46–7.49 (m, 2H), 7.34 (t, $J$ = 7.2 Hz, 1H), 7.21–7.23 (m, 2H), 7.09 (d, $J$ = 2.4 Hz, 1H), 6.98 (dd, $J$ = 8.4 Hz, 1.8 Hz, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 168.4, 162.7, 149.9, 142.3, 131.3, 129.7, 126.5, 121.5, 120.2, 118.0, 110.5; IR (neat): $\nu_{max}$ 3202, 1693, 1487, 1192, 1081, 771 cm$^{-1}$; HRMS (ESI, $m/z$) calcd for $C_{13}H_9ClO_3Na$ $[M + Na]^+$: 271.0138; found: 271.0151.

**Phenyl 2-hydroxy-4-nitrobenzoate, 2s, Scheme 2.** The same general procedure was followed by using 4-nitro-2-phenoxybenzoic acid (26.0 mg, 0.1 mmol, 1.0 equiv.), silver nitrate (0.9 mg, 0.005 mmol), potassium persulfate (40.5 mg, 0.15 mmol, 1.5 equiv.) and potassium trifluoroacetate (30.5 mg, 0.2 mmol, 2.0 equiv.). Column chromatography ($SiO_2$, eluting with 9 : 1 hexane–ethyl acetate) afforded the desired product as a yellowish solid, (13.5 mg, 52%), mp 146–148 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 10.75 (s, 1H), 8.29 (d, $J$ = 8.4 Hz, 1H), 7.90 (d, $J$ = 1.8 Hz, 1H), 7.81 (dd, $J$ = 8.4 Hz, 1.8 Hz, 1H), 7.50 (t, $J$ = 7.2 Hz, 2H), 7.37 (t, $J$ = 7.8 Hz, 1H), 7.24–7.26 (m, 2H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 167.6, 162.5, 152.5, 149.6, 131.7, 129.8, 126.9, 121.3, 116.6, 113.7, 113.3; IR (neat): $\nu_{max}$ 1690, 1527, 1208, 781 cm$^{-1}$; HRMS (ESI, $m/z$) calcd for $C_{13}H_9NO_5Na$ $[M + Na]^+$: 282.0378; found: 282.0354.

**Phenyl 2-hydroxy-5-nitrobenzoate, 2t, Scheme 2.** The same general procedure was followed by using 5-nitro-2-phenoxybenzoic acid (26.0 mg, 0.1 mmol, 1.0 equiv.), silver nitrate (0.9 mg, 0.005 mmol), potassium persulfate (40.5 mg, 0.15 mmol, 1.5 equiv.) and potassium trifluoroacetate (30.5 mg, 0.2 mmol, 2.0 equiv.). Column chromatography ($SiO_2$, eluting with 9 : 1 hexane–ethyl acetate) afforded the desired product as a yellowish solid, (13 mg, 50%), mp 149–151 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 11.19 (s, 1H), 9.05 (d, $J$ = 2.4 Hz, 1H), 8.43 (dd, $J$ = 9.0 Hz, 3.0 Hz, 1H), 7.50 (t, $J$ = 7.8 Hz, 2H), 7.38 (t, $J$ = 7.8 Hz, 1H), 7.26 (d, $J$ = 7.8 Hz, 2H), 7.18 (d, $J$ = 9.6 Hz, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 167.7, 166.6, 149.6, 140.2, 131.1, 129.8, 127.0, 126.9, 121.3, 118.9, 111.7; IR (neat): $\nu_{max}$ 1697, 1624, 1514, 1333, 1194, 751 cm$^{-1}$; HRMS (ESI, $m/z$) calcd for $C_{13}H_{10}NO_5$ $[M + H]^+$: 260.0559; found: 260.0574.

**4-Chlorophenyl 2-hydroxy-5-nitrobenzoate, 2u, Scheme 2.** The same general procedure was followed by using 2-(4-chlorophenoxy)-5-nitrobenzoic acid (29.5 mg, 0.1 mmol, 1.0 equiv.),

silver nitrate (0.9 mg, 0.005 mmol), potassium persulfate (40.5 mg, 0.15 mmol, 1.5 equiv.) and potassium trifluoroacetate (30.5 mg, 0.2 mmol, 2.0 equiv.). Column chromatography ($SiO_2$, eluting with 9 : 1 hexane–ethyl acetate) afforded the desired product as a white solid, (13 mg, 45%), mp 148–150 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 11.07 (br s, 1H), 9.02 (d, $J$ = 2.4 Hz, 1H), 8.44 (dd, $J$ = 9.0 Hz, 3.0 Hz, 1H), 7.46–7.48 (m, 2H), 7.20–7.23 (m, 2H), 7.18 (d, $J$ = 9.0 Hz, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 167.4, 166.6, 148.0, 140.2, 132.4, 131.3, 129.9, 127.0, 122.7, 119.0, 111.4; IR (neat): $\nu_{max}$ 1696, 1482, 1340, 1196, 723 cm$^{-1}$; HRMS (EI, $m/z$) calcd for $C_{13}H_8ClNO_5$ $[M]^+$: 295.0061; found: 295.0059.

### General experimental procedure for the carboxyl radical-assisted 1,5-aryl migration through Smiles rearrangement using 2-(phenylthio)benzoic acids, Scheme 3

To an oven-dried 15 mL sealed tube, a mixture of 2-(phenylthio)benzoic acid (0.2 mmol, 1.0 equiv.), silver nitrate (1.7 mg, 0.01 mmol) and potassium persulfate (81 mg, 0.3 mmol, 1.5 equiv.) was taken and dry MeCN (4.0 mL) was added to it. After flushing with nitrogen, the vessel was sealed with a screw cap. The reaction mixture was allowed to stir for 36 h at 130 °C. After completion (as indicated by TLC), the reaction mixture was cooled to room temperature. Then the reaction mixture was poured into water (30 mL) and extracted with ethyl acetate (40 mL). The organic layer was washed with water (10 mL × 2) and brine (10 mL), dried over anhydrous $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography using ethyl acetate–hexane as eluent to afford the desired product.

**Diphenyl 2,2′-disulfanediyldibenzoate, 4a, Scheme 3.** The same general procedure was followed by using 2-(phenylthio) benzoic acid (46.0 mg, 0.2 mmol, 1.0 equiv.), silver nitrate (1.7 mg, 0.01 mmol), potassium persulfate (81 mg, 0.3 mmol, 1.5 equiv.). Column chromatography ($SiO_2$, eluting with 9 : 1 hexane–ethyl acetate) afforded the desired product as a white solid, (37.5 mg, 82%), mp 104–106 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.34 (dd, $J$ = 7.8 Hz, 1.8 Hz, 2H), 7.86 (dd, $J$ = 8.4 Hz, 0.6 Hz, 2H), 7.53 (td, $J$ = 8.4 Hz, 1.8 Hz, 2H), 7.46–7.49 (m, 4H), 7.29–7.36 (m, 8H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 164.9, 150.6, 141.4, 133.7, 132.0, 129.6, 126.6, 126.14, 126.07, 125.7, 121.7; IR (neat): $\nu_{max}$ 1718, 1488, 1246, 1194, 1036, 743 cm$^{-1}$; HRMS (ESI, $m/z$) calcd for $C_{26}H_{18}O_4S_2Na$ $[M + Na]^+$: 481.0544; found: 481.0548.

**Diphenyl 2,2′-disulfanediylbis(4-fluorobenzoate), 4b, Scheme 3.** The same general procedure was followed by using 4-fluoro-2-(phenylthio)benzoic acid (50.0 mg, 0.2 mmol, 1.0 equiv.), silver nitrate (1.7 mg, 0.01 mmol), potassium persulfate (81 mg, 0.3 mmol, 1.5 equiv.). Column chromatography ($SiO_2$, eluting with 9 : 1 hexane–ethyl acetate) afforded the desired product as a white solid, (33.5 mg, 68%), mp 122–124 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.37 (dd, $J$ = 8.4 Hz, 6.0 Hz, 2H), 7.55 (dd, $J$ = 9.6 Hz, 2.4 Hz, 2H), 7.45–7.48 (m, 4H), 7.31 (t, $J$ = 7.2 Hz, 2H), 7.26–7.27 (m, 4H), 7.02–7.05 (m, 2H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 166.1 (d, $J$ = 256.5 Hz), 164.1, 150.4, 144.8 (d, $J$ = 9.0 Hz), 134.8 (d, $J$ = 9.0 Hz), 129.6, 126.3, 122.8 (d, $J$ = 3.0 Hz), 121.7, 113.4 (d, $J$ = 22.5 Hz), 113.1 (d, $J$ = 27.0 Hz); IR (neat): $\nu_{max}$ 1720, 1578, 1481, 1250, 1189, 1075, 746 cm$^{-1}$; HRMS (ESI, $m/z$) calcd for $C_{26}H_{16}F_2O_4S_2Na$ $[M + Na]^+$: 517.0356; found: 517.0336.

**Bis(4-chlorophenyl) 2,2′-disulfanediyldibenzoate, 4c, Scheme 3.** The same general procedure was followed by using 2-(4-chlorophenylthio)benzoic acid (53.0 mg, 0.2 mmol, 1.0 equiv.), silver nitrate (1.7 mg, 0.01 mmol), potassium persulfate (81 mg, 0.3 mmol, 1.5 equiv.). Column chromatography ($SiO_2$, eluting with 9 : 1 hexane–ethyl acetate) afforded the desired product as a white solid, (33 mg, 63%), mp 160–162 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.31 (dd, $J$ = 7.8 Hz, 1.2 Hz, 2H), 7.85 (d, $J$ = 8.4 Hz, 2H), 7.53 (td, $J$ = 8.4 Hz, 1.2 Hz, 2H), 7.43 (d, $J$ = 9.0 Hz, 4H), 7.35 (t, $J$ = 7.2 Hz, 2H), 7.24 (d, $J$ = 8.4 Hz, 4H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 164.6, 149.0, 141.4, 133.9, 132.1, 131.6, 129.6, 126.2, 126.1, 125.8, 123.1; IR (neat): $\nu_{max}$ 1720, 1485, 1248, 1199, 1036, 736 cm$^{-1}$; HRMS (ESI, $m/z$) calcd for $C_{26}H_{16}Cl_2O_4S_2Na$ $[M + Na]^+$: 548.9765; found: 548.9767.

**Di-*p*-tolyl 2,2′-disulfanediyldibenzoate, 4d, Scheme 3.** The same general procedure was followed by using 2-(*p*-tolylthio) benzoic acid (49.0 mg, 0.2 mmol, 1.0 equiv.), silver nitrate (1.7 mg, 0.01 mmol), potassium persulfate (81 mg, 0.3 mmol, 1.5 equiv.). Column chromatography ($SiO_2$, eluting with 9 : 1 hexane–ethyl acetate) afforded the desired product as a white solid, (29 mg, 60%), mp 147–149 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.32 (dd, $J$ = 7.8 Hz, 1.2 Hz, 2H), 7.85 (dd, $J$ = 8.4 Hz, 0.6 Hz, 2H), 7.51 (td, $J$ = 8.4 Hz, 1.2 Hz, 2H), 7.34 (td, $J$ = 8.4 Hz, 1.2 Hz, 2H), 7.26 (d, $J$ = 8.4 Hz, 4H), 7.17 (d, $J$ = 9.0 Hz, 4H), 2.40 (s, 6H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 165.1, 148.3, 141.3, 135.8, 133.6, 132.0, 130.0, 126.7, 126.1, 125.6, 121.4, 20.9; IR (neat): $\nu_{max}$ 1717, 1504, 1247, 1193, 1031, 736 cm$^{-1}$; HRMS (ESI, $m/z$) calcd for $C_{28}H_{22}O_4S_2Na$ $[M + Na]^+$: 509.0857; found: 509.0851.

**Diphenyl 6,6′-disulfanediylbis(3-bromobenzoate), 4e, Scheme 3.** The same general procedure was followed by using 5-bromo-2-(phenylthio)benzoic acid (62.0 mg, 0.2 mmol, 1.0 equiv.), silver nitrate (1.7 mg, 0.01 mmol), potassium persulfate (81 mg, 0.3 mmol, 1.5 equiv.). Column chromatography ($SiO_2$, eluting with 9 : 1 hexane–ethyl acetate) afforded the desired product as a white solid, (37.5 mg, 61%), mp 210–212 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.45 (d, $J$ = 2.4 Hz, 2H), 7.68 (d, $J$ = 9.0 Hz, 2H), 7.62 (dd, $J$ = 9.0 Hz, 2.4 Hz, 2H), 7.47–7.50 (m, 4H), 7.34 (t, $J$ = 7.2 Hz, 2H), 7.27–7.29 (m, 4H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 163.8, 150.3, 140.1, 136.6, 134.7, 129.6, 128.0, 127.7, 126.4, 121.5, 119.6; IR (neat): $\nu_{max}$ 1726, 1454, 1289, 1241, 1193, 1077 cm$^{-1}$; HRMS (ESI, $m/z$) calcd for $C_{26}H_{16}Br_2O_4S_2Na$ $[M + Na]^+$: 636.8754; found: 636.8748.

**Diphenyl 6,6′-disulfanediylbis(3-fluorobenzoate), 4f, Scheme 3.** The same general procedure was followed by using 5-fluoro-2-(phenylthio)benzoic acid (50.0 mg, 0.2 mmol, 1.0 equiv.), silver nitrate (1.7 mg, 0.01 mmol), potassium persulfate (81 mg, 0.3 mmol, 1.5 equiv.). Column chromatography ($SiO_2$, eluting with 9 : 1 hexane–ethyl acetate) afforded the desired product as a white solid, (29.5 mg, 60%), mp

153–155 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.02 (dd, $J$ = 8.4 Hz, 2.4 Hz, 2H), 7.79 (dd, $J$ = 9.0 Hz, 4.8 Hz, 2H), 7.45–7.48 (m, 4H), 7.32 (t, $J$ = 7.2 Hz, 2H), 7.23–7.27 (m, 6H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 163.9 (d, $J$ = 1.5 Hz), 160.8 (d, $J$ = 246.0 Hz), 150.3, 136.2 (d, $J$ = 3.0 Hz), 129.6, 128.0 (d, $J$ = 7.5 Hz), 127.9 (d, $J$ = 6.0 Hz), 126.4, 121.5, 121.2 (d, $J$ = 22.5 Hz), 118.7 (d, $J$ = 24.0 Hz); IR (neat): $\nu_{max}$ 1727, 1460, 1243, 1193, 1029, 739 cm$^{-1}$; HRMS (ESI, $m/z$) calcd for $C_{26}H_{16}F_2O_4S_2Na$ $[M + Na]^+$: 517.0356; found: 517.0360.

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Organic LETTERS

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# Merging C−H Activation and Alkene Difunctionalization at Room Temperature: A Palladium-Catalyzed Divergent Synthesis of Indoles and Indolines

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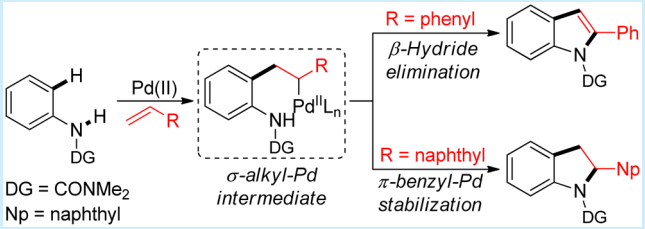
Supporting Information

**ABSTRACT:** A palladium-catalyzed 1,2-carboamination through C−H activation at room temperature is reported for the synthesis of 2-arylindoles, and indolines from readily available, inexpensive aryl ureas and vinyl arenes. The reaction initiates with a urea-directed electrophilic ortho palladation, alkene insertion, and $\beta$-hydride elimination sequences to provide the Fujiwara−Moritani arylation product. Subsequently, aza-Wacker cyclization, and $\beta$-hydride elimination provide the 2-arylindoles in high yields. Intercepting the common $\sigma$-alkyl-Pd intermediate, corresponding indolines are also achieved. The indoline formation is attributed to the generation of stabilized, cationic $\pi$-benzyl-Pd species to suppress $\beta$-hydride elimination.




Nitrogen-containing heterocycles, particularly indoles and indolines, are prevalent in numerous pharmaceuticals, natural products, agrochemicals, and functionalized materials.[1] Therefore, a significant effort has been devoted to their synthesis, and sustained progress has been made through Fisher,[2] Larock,[3] Buchwald,[4] and Hegedus[5] indole synthesis. In the past decade, the transition-metal-catalyzed C−H activation strategy has enabled the generation of indole moiety directly from anilines or protected anilines obviating rigorous prefunctionalizations. In this vein, two distinct strategies have been well explored: (a) intramolecular cyclization of *N*-arylenamines or -imines[6] and (b) intermolecular cyclization of anilines and alkynes.[7] We hypothesized that annulation of aniline derivatives with readily available and inexpensive olefins such as styrenes to afford 2-arylindoles and 2-arylindolines in intermolecular fashion will be synthetically attractive but challenging due to the facile $\beta$-hydride elimination. In fact, the potential of simple olefins was realized in the synthesis of *N*-arylindoles from diarylamines.[8] However, this methodology is limited due to the formation of inseparable mixture of regioisomers from unsymmetrical diarylamines and requires high temperature to occur. To exploit the full potential of C−H functionalization in the complex molecule synthesis,[9] development of expedient methods under mild conditions, particularly at room temperature,[10] is in high demand. Intrigued by the key mechanistic features, here we report a palladium-catalyzed divergent synthesis of 2-arylindole and indoline through a dehydrogenetive coupling of aryl urea and vinyl arene at room temperature.

Our initial screening with acetanilide and styrene in acetic acid at 110 °C was in vain due to the deleterious dimerization of styrene. Switching to other solvents such as 1,4-dioxane, the dimerization was reduced but not diminished. Therefore, we turned our attention to optimize this cascade reaction at room temperature. Cationic palladium complexes are known to undergo facile electrophilic palladation to aryl urea derivatives at room temperature.[10d,g−i] Gratifyingly, using *N*,*N*-dimethyl-*N*′-phenylurea and commercially available electrophilic Pd(tfa)$_2$, Pd(CH$_3$CN)$_4$(BF$_4$)$_2$ complexes, the yield of the desired product was improved at room temperature. Palladium(II) acetate, in the presence of excess TsOH, is known to generate highly electrophilic palladium mono- or bistosylate species in situ.[11] Interestingly, ubiquitous Pd(OAc)$_2$ in combination with TsOH and inexpensive 1,4-benzoquinone (BQ) was found to be optimal for the catalytic turnover. Other oxidants such as O$_2$, *N*-ligands/O$_2$, Cu(OAc)$_2$, AgOAc, and even DDQ were ineffective. Presumably, BQ has a dual role as ligand as well as oxidant in palladium(II) catalysis, and the redox process is anticipated to be accelerated under acidic conditions.[12] Other directing/protecting groups such as pivalate, tosylate, *N*,*N*-diethyl-*N*′-phenylurea, *N*-methyl, etc. were less effective in this case. After a rigorous screening (for details, see the Supporting Information), we found that 10 mol % of Pd(OAc)$_2$ in combination with 1.0 equiv of TsOH and 2.0 equiv of 1,4-benzoquinone as terminal oxidant provided 2-phenylindole in 82% yield at room temperature from 1.0 equiv of phenylurea and 1.5 equiv of styrene (entry 10, Table 1). During optimization, it was also found that water is detrimental to the reaction outcome, but dioxygen has little or no effect.

Subsequently, we explored the substrate scope under the optimized reaction conditions. A wide variety of functional

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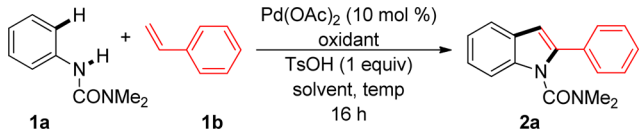
**Table 1. Optimization of the Reaction Conditions**[a]



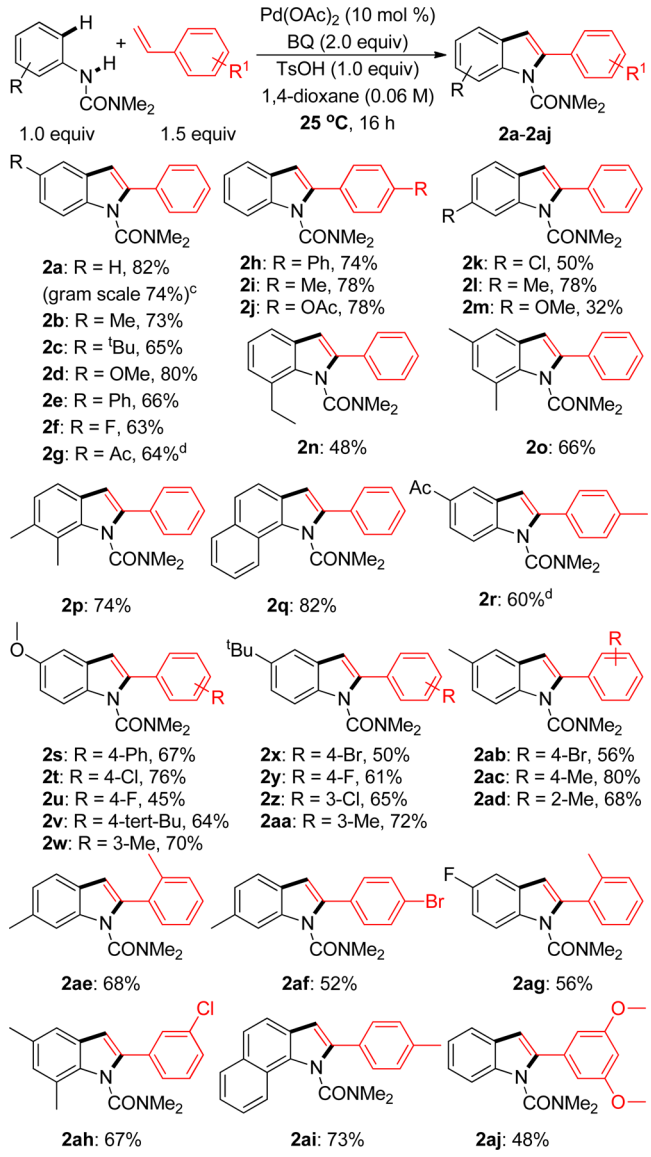

| entry | oxidant | solvent | temp (°C) | yield[b] (%) |
|---|---|---|---|---|
| 1 | $Cu(OAc)_2$ (1 equiv) | toluene | 110 | trace |
| 2 | AgOAc (1 equiv) | toluene | 110 | 8 |
| 3 | BQ (1 equiv) | 1,4-dioxane | 110 | 10 |
| 4 | BQ (1 equiv) | AcOH | 110 | 7 |
| 5 | BQ (1 equiv) | AcOH | 50 | 13 |
| 6 | BQ (1 equiv) | AcOH | 25 | 18 |
| 7 | BQ (2 equiv) | THF | 25 | 58 |
| 8 | BQ (2 equiv) | EtOAc | 25 | 77 |
| 9 | BQ (1 equiv) | 1,4-dioxane | 25 | 52 |
| **10** | **BQ (2 equiv)** | **1,4-dioxane** | **25** | **82** |
| 11 | DDQ (2 equiv) | 1,4-dioxane | 25 | trace |
| 12 | – | 1,4-dioxane | 25 | 12 |
| 13[c] | BQ (2 equiv) | 1,4-dioxane | 25 | 65 |
| 14 | BQ (3 equiv) | 1,4-dioxane | 25 | 80 |
| 15 | BQ (2 equiv) | 1,4-dioxane/AcOH (2:1) | 25 | 38 |

[a]All reactions were carried out in 0.1 mmol scale. [b]Yields refer to here are overall isolated yields. [c]2.0 equiv of TsOH was used.

groups on aniline as well as styrene were found to be compatible under this mild reaction protocol. Besides methoxy, alkyl, and aryl groups, halogens such as bromo (**2x**, **2ab**, **2af**, Scheme 1), chloro (**2k**, **2t**, **2z**, **2ah**, Scheme 1), and fluoro (**2f**, **2u**, **2y**, **2ag**, Scheme 1) remain intact which are useful for further cross-coupling reactions. Interestingly, the acyl group (**2g**, **2r**, Scheme 1) is well-tolerated under this protocol, which is a reactive functionality in the Fischer and Yoshikai method.[2,6f] An acid-sensitive −OAc (**2j**, Scheme 1) group is also stable, which demonstrates the mild nature of this protocol. The electronic nature has a prominent influence on the reaction outcome. In general, a moderate electron-donating group on the aniline has a positive influence due to the facile electrophilic palladation. However, highly electron-rich anilines are too reactive to provide the desired product. Similarly, neutral or moderately electron-rich and/or electron-defficient styrenes underwent annulation smoothly. Highly electron-deficient 3-nitrostyrene and pentafluorostyrene did not furnish any desired product, presumably due to the alkene deactivation for migratory palladium insertion. Interestingly, ortho-substituted anilines (**2n−q**, **2ah**, **2ai**, Scheme 1) also afforded good to high yields of the desired products, which are known to be difficult for electrophilic ortho palladation.[11] The meta-substituted anilines provided single regioisomeric indoles through ortho palladation from the sterically less hindered side (**2k−m**, **2ae**, **2af**, Scheme 1). All compounds are new entities and adequately characterized.[13]

From a mechanistic perspective, we realized that migratory insertion to the alkene results in an unstable $\sigma$-alkyl-Pd intermediate that could be intercepted for further functionalization.[14] The direct 1,2-carboamination strategy to generate indoline moiety was reported using norbornene[15] where $\beta$-hydride elimination is not feasible or using 1,3-dienes via $\pi$-allyl-Pd formation.[11] However, direct synthesis of 2-arylindolines through $\pi$-benzyl-Pd stabilization is not known. We chose

**Scheme 1. Substrate Scope of Indoles**[a,b]




[a]All reactions were carried out in 0.2 mmol scale. [b]Yields refer to the average of isolated yields of at least two experiments. [c]5 mol % of $Pd(OAc)_2$ was used. [d]Reaction time 30 h.

*p*-methoxy styrene as a model substrate to explore this divergent approach to indoline synthesis. Gratifyingly, the corresponding indoline was obtained in 48% isolated yield under the same reaction conditions (**3a**, Scheme 2). Remarkably, while *p*-acetoxystyrene (**2j**, Scheme 1) afforded indole selectively, the *p*-methoxy group favors indoline formation albeit in moderate yield. This subtle change in electronic nature leads to the generation of two distinct classes of compounds. This could be attributed to the formation of stabilized, cationic $\pi$-benzyl-Pd species that suppresses $\beta$-hydride elimination. Since naphthalenes have a better ability to stabilize $\pi$-benzyl-Pd species,[16] we decided to examine 1-vinylnaphthalene under the optimized conditions. As anticipated, the corresponding indoline was isolated in high yields with 1- and 2-vinylnaphthalenes. Remarkably, a number of urea derivatives with *ortho* substitution also provided the desired indolines in high yields (**3l−o**, Scheme 2).



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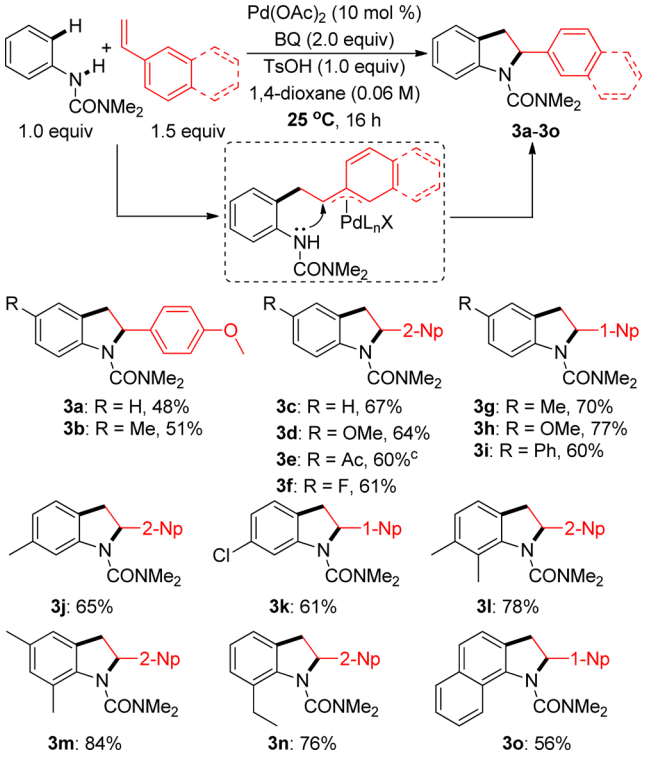
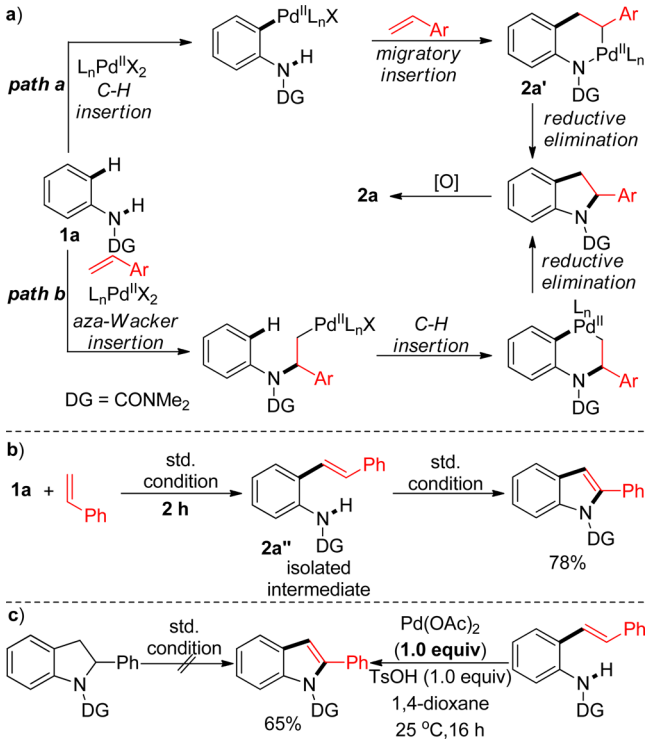
**Scheme 2. Substrate Scope of Indolines**[a,b]




[a]All reactions were carried out on a 0.2 mmol scale. [b]Yields refer to the average of isolated yields of at least two experiments. [c]Reaction time 30 h.

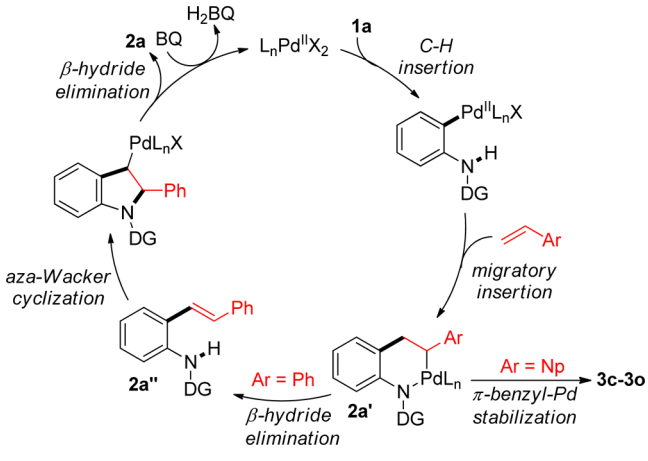
Mechanistically, the reaction may proceed in two distinct pathways. In path a, an electrophilic *ortho* palladation followed by migratory $\beta$-alkene insertion may lead to the intermediate **2a**′ (Scheme 3, a). Subsequently, reductive elimination to yield indolines and oxidation sequences may provide the desired 2-arylindoles. Alternatively, an initial aza-Wacker reaction followed by C−H arylation and oxidation cascade may lead to the desired product as shown in path b (Scheme 3, a). To understand the plausible mechanism, we performed several control experiments. From TLC, we observed that initially a polar, transient intermediate is formed which is converted into product during the reaction course. Therefore, the reaction was arrested after 2 h and the intermediate was isolated as Fujiwara−Moritani Heck arylation product **2a**″. Subsequently, this intermediate was subjected to the standard reaction conditions, and the desired 2-arylindole was obtained in 78% yield (Scheme 3, b). Therefore, the reaction may initiate through path a. To note, depending upon the $\pi$-benzyl-Pd stabilization ability, 8−12% corresponding indoles were also obtained along with the indolines (Scheme 2). Therefore, in the subsequent steps, either a concerted aza-Wacker cyclization followed by $\beta$-hydride elimination or initial 1,2-carboamination of styrenes to yield 2-arylindoline followed by oxidation to yield the desired product is plausible.[8] To probe this, 2-phenylindoline was synthesized separately and subjected to the standard conditions. The indoline remained intact, which eliminates the possibility of indoline formation/oxidation route (Scheme 3, c). It also demonstrates that indoles are kinetic in their origin through concerted $\beta$-hydride elimination. From the stoichiometric experiment it was observed that the Heck intermediate is converted to the corresponding indole in 65% yield with 1.0 equiv of $Pd(OAc)_2$/TsOH without 1,4-benzoquinone. Therefore, BQ may act as a ligand and oxidant to the palladium for catalytic turnover but may not be involved in the oxidation of indoline to indole directly.

**Scheme 3. Mechanistic Possibilities and Elucidations**




From all these control experiments it is speculated that the reaction proceeds through a C−H insertion/carbopalladation/cyclization/aromatization cascade. The indolines are formed in a convergent manner from the $\sigma$-alkyl-Pd intermediate through $\pi$-benzyl-Pd stabilization as depicted in Scheme 4.

**Scheme 4. Plausible Catalytic Cycle**




Finally, the corresponding indole and indoline urea were hydrolyzed with saturated solution of potassium hydroxide in refluxing ethanol to afford the 2-arylindole and indoline in 85% and 80% yield, respectively.

In conclusion, we have developed a mild reaction protocol for the synthesis of 2-arylindole and indoline derivatives from arylureas and -styrenes at room temperature. The indoles are



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formed through C−H insertion/1,2-carboamination/ $\beta$-hydride elimination cascade, whereas the indolines are obtained through C−H insertion and 1,2-carboamination via $\pi$-benzyl-Pd stabilization. The present intermolecular technique incorporates a wide range of starting materials using a ubiquitous and inexpensive catalytic combination. The catalytic conversion is also reproducible on a gram scale with lower catalyst loading. Therefore, we anticipate that this methodology will find many applications in academia as well as in industrial processes.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures, spectroscopic data, and $^{1}H$ and $^{13}C$ NMR spectra for all synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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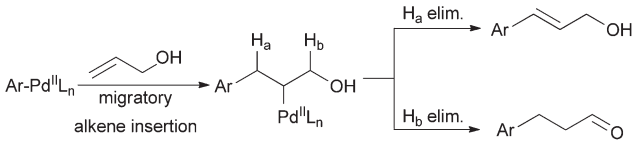
# Chemo-, regio-, and stereoselective Heck–Matsuda arylation of allylic alcohols under mild conditions†

Tohasib Yusub Chaudhari, Asik Hossian, Manash Kumar Manna and Ranjan Jana*

**Heck arylation with allylic alcohol is extremely challenging due to chemo-, regio-, and stereoselective scrambling. Here we report a mild protocol for the alcohol selective β- and α-arylation of allylic and cinnamyl alcohols respectively with aryldiazonium salts. The steric and electronic parameters of the alkene play a prominent role in the regioselectivity.**

Since its discovery, significant effort has been dedicated to the development of highly efficient and selective Heck–Mizoroki reaction for the arylation of alkenes.[1] Consequently, it has been recognized as one of the most powerful synthetic tools for C–C bond formation.[2] The extent of research on the Heck reaction over the past few decades has inculcated the false notion that Heck chemistry is now a mature area. However, the mechanistic understanding of subtle changes that dictate regioselectivity and β-hydride elimination is still limited.[3] Despite its robustness and efficiency, the Heck reaction involving aryl halides and triflates is mainly limited to the activated olefins such as acrylates, styrenes *etc*. In contrast, Heck arylation of electronically nonbiased olefin is still challenging due to sluggish alkene insertion and non-specific β-hydride elimination.[4] Similarly, Heck arylation of allylic alcohol is extremely challenging due to chemo-, regio-, and stereochemical scrambling and double bond isomerization (Scheme 1).[5]

Mechanistically, after oxidative addition of palladium(0)- to the aryl electrophile, a migratory β-alkene insertion occurs to generate an unstable σ-alkyl-Pd species. Subsequently, random β-hydride elimination (either $H_a$ or $H_b$, Scheme 1) leads to the formation of a mixture of products, which limits its synthetic utility. Therefore, a mild reaction protocol that controls β-hydride elimination is extremely useful in regio- and chemoselective arylation of allylic alcohols. In general, oxidative addition to the aryl electrophiles such as aryl halides, triflates




**Scheme 1** Chemoselectivity in Heck arylation with allylic alcohol.

*etc*. is the rate limiting step, which requires high temperature, ligands, bases *etc*.[6] The harsh reaction conditions lead to the non-specific arylation, β-hydride elimination, and double bond isomerizations. After the first report by Matsuda and co-workers in 1977, arenediazonium salts have been exploited as reactive aryl halide surrogates in Pd-catalyzed cross-coupling reactions.[7] The Sengupta,[8] Genêt,[9] Correia,[10] Felpin[11] and other groups[12] have contributed substantially to the Heck–Matsuda arylation of olefins. Recently, the Sigman group has accomplished styrenyl selective arylation of electronically non-biased olefins with aryl diazonium salts.[13] Due to the facile oxidative addition to the aryldiazonium salts, the cross-coupling took place under mild reaction conditions, without any additional ligands or bases. Therefore, we decided to optimize Heck–Matsuda arylation of allylic alcohols with aryldiazonium salts. Although, there are few reports of Heck arylation with allyl or crotyl alcohol,[14] most of them provide a mixture of aldehyde(or ketone) and alcohol. In addition, Heck–Matsuda arylation with β-substituted alkenes especially cinnamyl alcohols is underexplored.[15] Heck arylation of cinnamyl alcohol with expensive aryl iodide has been reported by the Cacchi group.[16] However, a high reaction temperature, a stoichiometric base, and a longer reaction time were required to afford only a low to moderate yield of the desired products. Here we report an alcohol selective, β- and α-arylation of allyl and cinnamyl alcohols respectively using aryldiazonium salts (Scheme 2). From the systematic study, we have observed that besides steric factors, electronic parameters of the alkene also play an important role in regioselectivity.

To begin, we tested simple allyl alcohol and phenyldiazonium salt with a catalytic amount of $Pd_2dba_3$. A rapid efferve-

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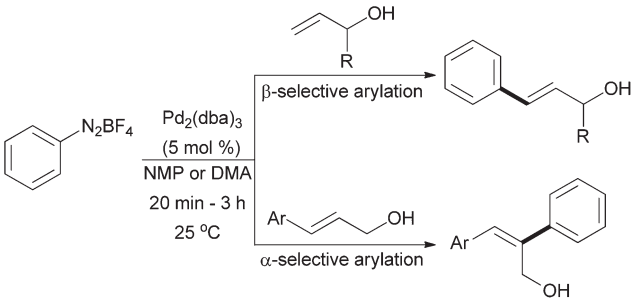


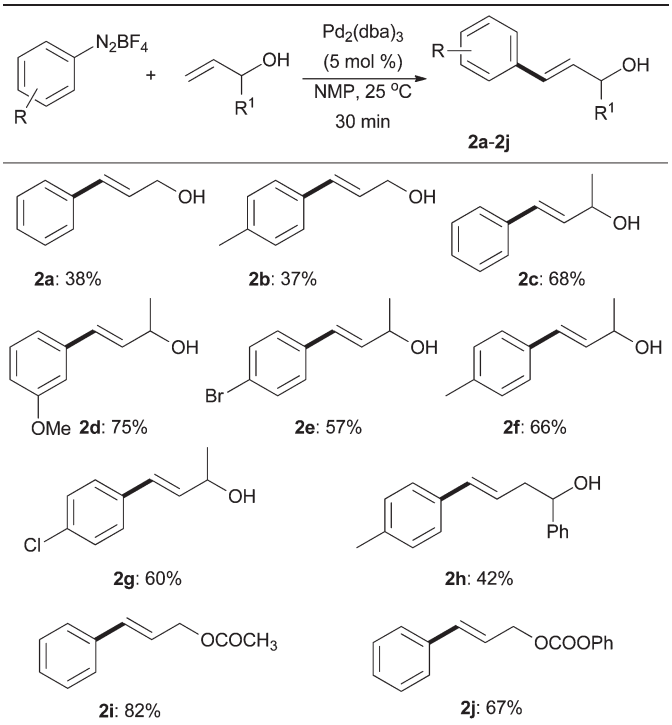

Scheme 2 Regioselective arylation with aryldiazonium salts.

scence of nitrogen was observed after the addition of the catalyst in DMF at room temperature. Unfortunately, the yield of the desired cinnamyl alcohol was low (~20%) although, all starting material was consumed. Next, we screened several solvents which are frequently used in the Heck–Matsuda reaction, *e.g.* MeOH, $CH_3CN$, DMA, NMP *etc*. It was observed that amide solvents are superior and NMP is the best solvent for this transformation. It was also found that a tetrafluoroborate counterion is crucial for the reaction outcome. Presumably, in addition to the improved stability of the diazonium moiety, its non-coordinating nature imparts electrophilicity to the metal center for the facile alkene insertion.[17] The amide solvent stabilizes the incipient electrophilic Pd-species which is formed through oxidative addition.[18] All of our screening with simple allyl alcohol afforded only a moderate yield of the desired products (**2a**, **2b**, Table 1) and a substantial amount of oligomerization was observed. However, using secondary allylic alcohols, the yield of the arylation product was increased. The arylation with 3-butene-2-ol afforded the corresponding alcohol in good to high yields (**2c–2g**, Table 1).

A homoallylic alcohol also underwent the Heck–Matsuda reaction affording moderate yield of the arylation product (**2h**, Table 1). Interestingly, protected allyl alcohols such as allyl acetate (**2i**, Table 1) and allyl carbonate (**2j**, Table 1) underwent smooth arylation providing β-arylation in high yields. In general, these substrates are unstable under Pd(0)-catalysis *e.g.* Tsuji–Trost conditions.[19] This demonstrates the mild nature of these reaction conditions.

Next we turned our attention to the arylation of cinnamyl alcohol derivatives. From our previous experience with allyl alcohol we realized that cinnamyl alcohol may lead to the selective α-arylation due to steric hindrance with the terminal phenyl group. That said, we investigated the analogous Heck–Matsuda reaction with cinnamyl alcohol and arenediazonium tetrafluoroborate. Gratifyingly, a good yield of the arylation product was obtained simply by changing the solvent to DMA. As anticipated, the α-arylation was obtained exclusively to afford (*Z*)-2-3-diarylallylic alcohol. The stereochemistry of the arylation product was assigned by NOESY experiment and comparison with literature reports (see the ESI†).[20] A number of cinnamyl alcohol derivatives and arenediazonium salts were examined for the coupling reaction, and a wide range of functional groups such as methoxy (**3b**, **3d**, **3m**, **3n**, **3r**, Table 2), nitro (**3c**, **3e**, **3f**, **3m**, **3o**, Table 2), ester (**3k**, Table 2), bromo (**3f**, **3h**, **3p**, Table 2), chloro (**3i**, **3j**, Table 2), and even iodo (**3l**, Table 2), were compatible under the reaction conditions. However, reaction with *p*-iodophenyldiazonium (**3l**) also gave ~10% of the corresponding aldehyde *via* double bond isomerization. These halogen substituents are useful for further cross-couplings. Gratifyingly, a sterically hindered mesitylenediazonium salt provided excellent yield of the arylation products (**3n–3r**, Table 2). Interestingly, no arylation was observed with cinnamyl acetate which indicates that besides steric effects the free hydroxyl group also may have a role in regioselectivity through coordination with the metal center.

Table 1 Substrate scope with allylic alcohols[a,b]

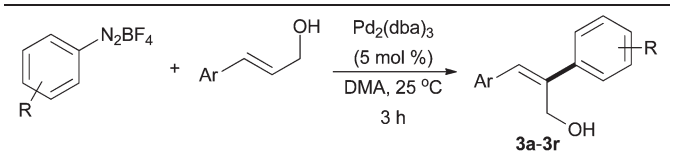



[a] The reaction was performed on a 0.2 mmol scale. [b] Yield refers to the isolated pure product.

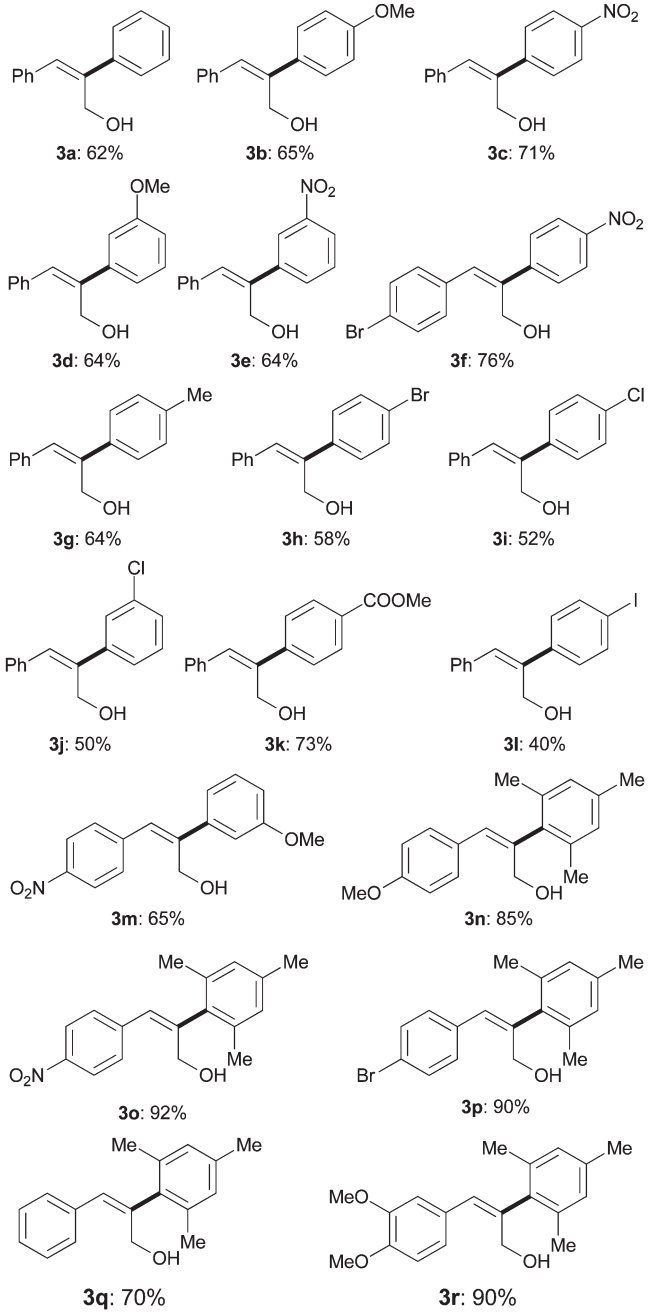
Finally, we carried out a sequential Heck–Matsuda arylation to afford (*Z*)-2-3-diarylallylic alcohol. Since allyl alcohol provided low yield, we took allyl acetate for the β-arylation followed by hydrolysis to provide cinnamyl alcohol derivative, **4**. The subsequent α-arylation provided **3f** in 76% yield (Scheme 3a). Since halogens are compatible with our reaction conditions, we have demonstrated a sequential Heck/Suzuki coupling reaction. Initially, the Heck reaction was performed with 3-butene-2-ol and 4-bromo-phenyldiazonium salt to give **2e**. The product was further cross-coupled with phenyl boronic acid to yield **5** (Scheme 3b). We have also showed that synthetically useful β,β- and β,α-diarylallylic alcohols can easily be accessed through the Heck–Matsuda reactions. The arylation of cinnamic ester occurs at the β-position selectively,[21] and the

**Table 2** Substrate scope with cinnamyl alcohols[a,b]

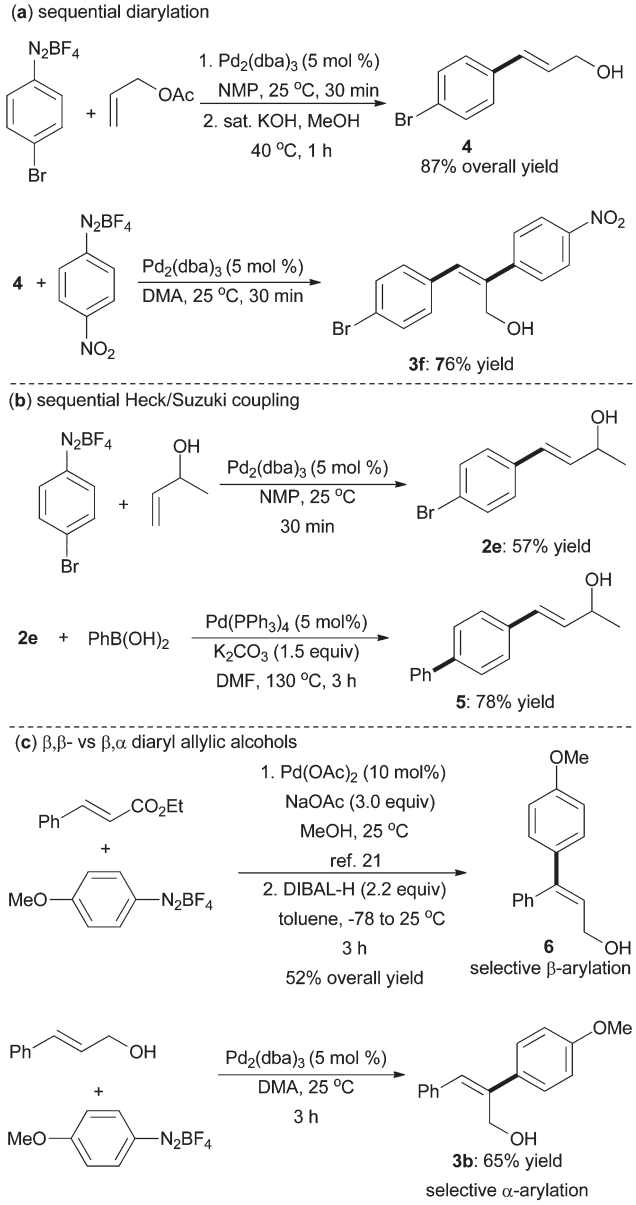



**3a-3r**




[a] The reaction was performed on a 0.2 mmol scale. [b] Yield refers to the isolated pure product.

ester is reduced to the corresponding alcohol with DIBAL-H, whereas, in this present protocol cinnamyl alcohol leads to the α-arylation product selectively (Scheme 3c). This phenomenon




**Scheme 3** Synthetic manipulations of the present protocol.

demonstrates that besides steric parameters, electronic nature of the alkene also plays an important role in regioselective arylation.

## Conclusions

We have developed a mild protocol for the alcohol-selective Heck–Matsuda arylation of allylic alcohols in a highly regio- and stereoselective manner. In sharp contrast to the allylic alcohols, a selective α-arylation of the cinnamyl alcohols was observed to afford (*Z*)-2-3-diarylallylic alcohol. Taking advantage of mild reaction conditions, we have also demonstrated the sequential diarylation and Heck/Suzuki coupling. From

the systematic study, we observed that besides steric factors, electronic parameters also play an important role in regioselectivity. Therefore, selective β,β- and β,α-diaryl allylic alcohols have been synthesized from cinnamic ester and cinnamyl alcohol respectively.

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